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HYPERTENSION

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HYPERTENSION

By

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BALTIMORE
THE WILLIAMS & WILKINS COMPANY
1930

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Made in the United States of America

Published May, 1930

COMPOSED AND PRINTED AT THE
WAVERLY PRESS, INC.
FOR
THE WILLIAMS & WILKINS COMPANY
BALTIMORE, Md.

TO MY WIFE

A tribute to her endurance
while this book was
being written

IT IS almost impossible to exaggerate the influence which our knowledge of the vasomotor system, springing as it does from Bernard's researches as from its fount of origin, has exerted, is exerting, and in widening measure will continue to exert, on all our physiological and pathological conceptions, on medical practice, and on all the conduct of human life. There is hardly a physiological discussion of any width in which we do not sooner or later come upon vasomotor questions. . . . . And if, passing the insecure and wavering line which parts health from illness, we find ourselves dealing with inflammation or with fever, or with any of the disordered physiological processes which constitute disease, we shall find, whatever be the tissue affected by the morbid conditions, that vasomotor influences have to be taken into account. The idea of vasomotor action is woven as a dominant thread into all the physiological and pathological doctrines of today; attempt to draw out that thread and all that would be left would appear as a tangled heap."—SIR MICHAEL FOSTER'S *Claude Bernard*. London, 1899.

PREFACE

Arterial hypertension as a primary disorder of vasomotor function is the theme of this book. The causative factors, the clinical manifestations and sequelae, and particularly the study and management of hypertension I have tried to present from the standpoint of functional pathology. My aim has been to follow that ideal of avoiding "the unnecessary too much and the dangerous too little," which Munk well says is so essential in regulating and making over the lives of those who carry the burden of persistent high blood pressure.

For a clinician to venture from beaten paths in the domain of hypertension, as indeed of all inner medicine, is perilous, at least to his self-esteem. His experience of the bedside and consulting room is rather overwhelmed by the contributions of the ancillary sciences. The mechanisms of cell permeability, the behavior of colloids, the physico-chemical reactions underlying circulatory insufficiency, hold, he is convinced, those secrets of pathologic function for which he seeks explanation. These and other biologic fields seem far more promising than his efforts to relieve the ills of patients who are wont to vanish concomitantly with their symptoms and reappear eventually a little—or much—too late. Of course this is only an illusion. After all is said and done, science must be translated by the physician according to his patient's needs, and clinical observation will always be indispensable.

Considerably more dangerous, on the whole, than this wandering in the by-ways of experiment and hypothesis, is the sterility of attitude toward hypertension still shown by not a few pathologists and clinical teachers, "whose outlook on physiology," Wiggers writes, "has not advanced beyond the time of Ludwig." For these, and the generations of students whom they have influenced, the functional point of view is sure, I believe, to bring a new sense of values and the feeling that the problems of hypertension are not impregnable.

Of debts and acknowledgments to others, the man who writes from the clinic and every day practice has many. My own obligations in respect to hypertension begin with Janeway, were continued later at Sloane under Mosenthal—all alumni of the old hospital remember the "Forty-niners"—and as "chronic nephritis" was giving way to "hyperpiesia" and "essential hypertension," on the wards of New York Hospital under Conner and Foster. An introduction at that time by Dr. Conner to Allbutt's two

volumes was one of life's great experiences! Since then, contact with students, undergraduate and graduate, in several medical schools began slowly to lead to the belief that a short and simple account of the background of hypertension and the admirable work that many men in all parts of the world are constantly doing, might be of help to the practitioner.

To my colleagues at Cornell and George Washington and in various medical societies and groups, I owe much in the way of stimulating discussion, as well as use of material. Dr. Buckner M. Randolph has given me free scope in the study of hypertensive patients in his wards. To the staff of the Surgeon-General's Library I have been as persistent a burden as high pressure for two years, but their good nature, like the resources of the Library, remains peerless. Janeway's accumulation of 1000 titles on blood pressure in 1915 could now easily be tripled; but after many rejections, I believe that the appended bibliography of over 500 titles will afford keys to the major literature of hypertension.

LESLIE T. GAGER.

Washington, D. C.
January, 1930.

CONTENTS

CHAPTER I

The Definition of Hypertension 1

CHAPTER II

The Historical Background of Hypertension 5

CHAPTER III

Hypertension and Renal Disease 10

CHAPTER IV

The Functional Basis of Hypertension 21

CHAPTER V

Chemical Factors in Hypertension 33

CHAPTER VI

The Incidence of Hypertension 49

CHAPTER VII

The Symptomatology of Hypertension 56

CHAPTER VIII

The Clinical Study of Hypertension 66

CHAPTER IX

Prognosis in Hypertension 88

CHAPTER X

The Treatment of Hypertension 96
I. General Measures 96
II. Specific Measures 110

Literature References 127

Index of Personal Names 149

Subject Index 155

ILLUSTRATIONS

FIG. 1. Chart illustrating the variability of high blood pressure 24
FIG. 2. Chart illustrating the fixation of high blood pressure 25
FIG. 3. Chart showing the effect of medical supervision on the course of hypertension, and also of sulphocyanate treatment 116
FIG. 4. Chart showing the effect of potassium sulphocyanate in an ambulant hypertensive patient 116
FIG. 5. Chart showing the effect of potassium sulphocyanate in an ambulant hypertensive patient 116

CHAPTER I

The Definition of Hypertension

Ludwig Traube was the first to describe increased arterial tension (473). With his clinical sense sharpened by the knowledge of the systemic effects of kidney disease and of the rise and fall of blood pressure which, at the hands of Bright and Ludwig, the new pathology and physiology of the second quarter of the nineteenth century had just developed, Traube at the bedside realized that by palpation there was revealed a physical change (*Spannung*) of the vessel wall clearly related to the state of intravascular pressure.

A generation later, the introduction of clinical sphygmomanometry shifted emphasis for the moment to the elevation of blood pressure. The element of vascular strain and stretching (*tendere*, to stretch) implied in Potain's "hypertension" receded into the background. The use of the word became purely clinical. As the synonym of high arterial blood pressure it implies no specific physiological mechanism or pathological foundation. This neutral position invites a wide point of view, though at the same time, it allows opportunity for the uncritical to make hypertension another of the catchwords of medicine.

Hypertonia, the term commonly employed in the clinics of continental Europe, does imply the conception of increased vascular tonus, and emphasizes in a definite way the fundamental importance of small vessel constriction in the causation of high blood pressure.

To hyperpiesia (πιέσις, pressure) the disciples of Allbutt still cling as the name "to connote not the high arterial pressure only, but the whole morbid series, not chronic renal disease, of which high arterial pressure is one term" (9). Introduced to mark a disease entity set apart by excessive arterial pressure "without the initiation, intercurrence or sequel . . . . of chronic renal disease in any of its forms," Allbutt's exposition of the malady hyperpiesia (and the process hyperpiesis) has helped in a large measure to revolutionize clinical thought, though the terms themselves pass into oblivion.

In practice, it appears that hypertension, hypertonia, and hyperpiesia are employed without any well defined, or intended, distinction. Certainly, peripheral resistance to blood flow on the basis of widespread functional or structural vascular change is recognized as the predominant factor in heightened arterial pressure (Volhard), and while the necessity of an efficient

myocardium, as the source of dynamic energy, is granted, this (93) and the factors of blood mass and viscosity (88, 89, 90, 508) and velocity (204, 513) are relegated commonly to a position of distinctly secondary importance.

More than this, the acceptance of the point of view that elevation of arterial blood pressure is the result of arteriolar activity goes far to invalidate the traditional division of hypertension into a primary, simple, genuine, or essential type on the one hand, and a secondary form on the other. With few exceptions all hypertension becomes a manifestation of vasoconstriction (386) excessive in degree or extent. It rests upon fundamental derangements of function, the nature and mechanism of which, as of all other biological processes, are susceptible of ultimate analysis.

Arterial hypertension may be defined as a state of the circulation in which intravascular blood pressure rises above normal limits.

Lesser as well as greater circulation may be affected, the one independently of the other. But since the mechanism of pulmonary hypertension (340) is mainly one of obstruction to blood flow from obvious anatomic disease—such as mitral stenosis and emphysema—it is the aortic system which presents the problems of the causation of arterial hypertension.

This rise of pressure may be temporary, intermittent, or chronic. It may involve systolic pressure, diastolic pressure, or both. If transient, the elevation may subside with the disappearance of the stimulus which called forth the vasoconstriction. Or as the stimuli grow more frequent, or the vascular response more ready, the hypertension either rapidly, even fulminantly, or by slow gradations, goes on to permanence. Its level tends to mount constantly higher, though in the slow progression of a "benign" hypertension, wide fluctuations are most striking, and in the malign type an end point of absolute fixation, a complete "setting" of the pressure, is rarely attained.

What are the normal limits of blood pressure? Biologically, the optimum level is that which goes with the highest state of health, and conversely with the lowest mortality, for each year of life. For such facts, the statistics of life insurance medicine are the source.

From Hunter's (218) compilation of the blood pressures of nearly a quarter million healthy persons from ten years to sixty years inclusive, an authoritative standard is set for the average variations with age. From an average systolic and diastolic blood pressure of 120/80 at the age of twenty years, the level increases to 135/89 at the age of sixty years. There is a rise in each half-decade of approximately 2 mm. Hg in the systolic pressure and of 1 mm. in diastolic and pulse pressures. Within such narrow bounds are the physiologic limits of blood pressure.

Further, life insurance statistics show the direct proportion of mortality

increase to elevation of pressure above standard for the age. In Fisher's (158) series of 4165 cases of hypertension, without other serious impairment, the extra mortality was 36.1 per cent when the blood pressure was 10 to 14 mm. over the standard. The added mortality became 83.8 per cent when the systolic pressure exceeded the average for age by 15 to 24 mm., and rose to 314.7 per cent above the expected mortality when the pressure was 50 mm. or above the standard. In a series of 2838 hypertensive persons, Rogers and Hunter (420) found an extra mortality of 46 per cent when the pressure was 10 to 25 mm. above the standard, rising to 148 per cent when the elevation was 36 to 50 mm. When obesity, mitral insufficiency, and albuminuria were added to the high pressure the extra mortality became 211, 220 and 290 per

TABLE 1

The average variations of blood pressure (after Hunter's compilation of observations on a quarter million healthy Americans)

AGE	SP	DP	PP
10	103	70	33
15	113	75	38
20	120	80	40
25	122	81	41
30	123	82	41
35	124	83	41
40	126	84	42
45	128	85	43
50	130	86	44
55	132	87	45
60	135	89	46

cent, respectively. These are impressive figures. They reveal the fallacy of empirical and arbitrarily selected standards of blood pressure in clinical medicine and explain the constant lowering of that level of pressure, which if persistent, means the beginning of hypertension and its unfavorable complications.

This pathogenetic level, for systolic pressure, may be conservatively set at 140 mm. up to the age of forty years, and with somewhat greater leniency, at 150 mm. after forty years. Diastolic hypertension is more difficult to fix, because extensive data of mortality associated with diastolic pressure have not become available. It is likely that 90 mm. Hg may be a conservative dividing line, certainly below the age of forty years, and possibly thereafter. In practical use, this level does not result in a striking disproportion

of diastolic to systolic hypertension. The level of 100 mm. selected by some authors appears too high even for the last decades of life (414a).

With caution, however, and only after adequate opportunity for observation is a borderline patient to be rated as hypertensive. Equanimity does not usually go with the first visit to the consulting room, and the spontaneous variability of blood pressure is remarkable (147, 261, 344, 372, 450). Abundant clinical experience supports the functional conception that incipient hypertension is the expression—often very labile—of an active arteriolar response to many factors, physical, chemical, nervous and psychic. To borrow Aschoff's remark concerning arteriosclerosis, hypertension also "is the resultant of numerous variables."

CHAPTER II

The Historical Background of Hypertension

For first principles, as well as for method, the science of hemodynamics sends its roots back to the English garden where Stephen Hales (185), "rector of Farrington, minister of Teddington," turned from plant physiology "to find out the real force of the blood in the arteries." "Not only in animals of different species but also in animals of the same kind . . . . and even in the same animal," Hales wrote, with insight, in 1733, "the Force of the Blood in its vessels is continually varying, according to the different kinds and quantities of foods, the various distances of time after taking food, the more or less plethoric state of the blood Vessels, also from Exercise, Rest, different states of Vigour or Vivacity of the animal and many other circumstances."

Not far wrong was Hales' deduction, from animal experiments carried out over a quarter of a century, that the blood led from the carotid of man into a straight tube would rise 7½ feet (approximately 200 mm. Hg). And his use of mercury and the U-tube in the study of "vegetable staticks" was the germ of the great practical advance in manometry which Poiseuille applied a hundred years later to the determination of the aortic force of the heart (405).

A graduate of the Ecole Polytechnique a few years before Pasteur, Jean L. M. Poiseuille stands a model for those who maintain that the study of mathematics and physics is the best preparation for medicine. In his Paris thesis, in 1828, he exposed the absurdities of Keill's and Borelli's estimates of the force of the heart beat—the one 5 ounces, the other 180,000 pounds—and recognized the error from blood loss inherent in the method of Hales. With his compact hemodynamometer, and the use of sodium carbonate as anti-coagulant in the connecting cannula, for the horse, dog and ram he found that the aortic pressure rose to 140 to 180 mm. Hg. Approximately the same levels he believed to exist in man.

By causing a float to rest on the mercury column and write on a revolving drum, Ludwig, (294) in 1847, "applied the graphic method to physiology." The study of blood pressure straightway made its appeal to the clinic. Need of a method for the bedside led to the sphygmographs of Marey and Vierordt, and in the hands of an observer like Mahomed (303) many of the clinical associations and problems of high pressure were first defined.

Unable to record the volume changes in the forearm by the plethysmograph as indices of blood pressure variation (1876), von Basch introduced the clinical sphygmomanometer (53) in 1883. Of this epoch making instrument Janeway (224) has said, "In two fundamental respects it differed from all that had preceded it. One was the employment of a bag containing fluid as the compressing mechanism, thus obtaining pressure per unit of surface for the first time; the other was the use of a mercury manometer for the measurement of the pressure within the bag necessary to wholly compress the artery. In this way he made possible a comparison of results with the direct methods of the physiologist."

The evolution of sphygmomanometry has continued as difficulties in technique, as well as violations of physiological principle, led to important modifications. The method of circular compression of the artery introduced by Riva-Rocci in 1896 and by Hill in 1897 replaced the frequently ineffectively applied pelotte; the substitution by von Recklinghausen in 1901 of the cuff 12 cm. in width removed a source of inaccurately high readings with narrower armlets; and finally, in 1905, the auscultatory method of Korotkoff made possible the easy determination of both systolic and diastolic pressures and established the clinical study of blood pressure upon its modern basis. Physiologists are now agreed that the method of indirect sphygmomanometry gives records of intraarterial pressure which are essentially free from faults of technique or errors in dynamics (300, 322).

By the time a practical method for determining blood presure had been developed, clinical medicine was well prepared to appreciate its significance. Symptoms which are those of high blood pressure had been recorded by the Greeks under the name of plethora. Galen surmised the nutritive function of blood flow in the tissues. But the "pulsus durus" had no physiological meaning because Harvey and Malpighi were yet to explain the circulation.

A broad conception of systemic vascular disease came into being only when Bright (85) sought a reason for the hypertrophy of the heart which he found in half his patients with albuminous urine and diseased kidneys. "The two most ready solutions appear to be," he wrote in 1837, "either that the altered quality of the blood affords irregular and unwonted stimulus to the organ immediately; or that it so affects the minute and capillary circulation as to render greater action necessary to force the blood through the distant subdivisions of the vascular system."

Bright it has been said, (434), began the story of hypertension and its consequences by writing its final chapter. The emphasis placed at the outset upon the kidney disease, by pathologist and physician alike, gave the hypothesis of the renal genesis of high blood pressure an authority which

dominated thought and practice. From his masterly clinical correlation of the tense pulse, cardiac enlargement and thrust, accentuated heart sounds, and the signs of kidney disease, Traube (473) deduced an elevation of arterial pressure which he explained through overfilling of the aortic system brought about by resistance to blood flow in the damaged kidneys. This hypothesis of an overloading of the greater circulation as a cause of hypertension, it is of interest to note, is inherent in the assumption that diminished blood content of the pulmonary system produces a state of imbalance between the two circuits, for which deep breathing is the suggested remedy (410).

To this purely mechanical theory, it was an easy step to join the idea of retention by the kidney of toxic substances, for both by the Bright school and by Ludwig, the decrease of urea in the urine and its increase in the blood had been noted in nephritic patients. Here was evidence for an "altered quality" of the blood and an explanation of hypertension as a compensatory mechanism for maintaining renal filtration. Thus began the search for increased or abnormal products of metabolism which might serve as pressor agents.

As account was taken of the variety of acute and chronic lesions described by Bright in the kidneys, it became evident that distinct entities were to be separated, and that some of them bore no relation to blood pressure. Bright's disease, Aschoff (34) declared in 1927, should be restricted to diffuse glomerular nephritis and the resulting secondary contracted kidney. Addis (5) calls all abnormalities in the rate of protein, blood cell and cast excretion Bright's disease, but recognizes practically that the hemorrhagic, arteriosclerotic and degenerative groups are separate entities.

Thickening of the arterial walls in chronic Bright's disease was discussed by Kirkes (248) in 1859, and Johnson (229) anticipated Ziegler and Löhlein in studying the vascular changes in the kidney, including the hypertrophy of the muscular layer, which he noted particularly in the afferent arterioles. His observation that the thickening was proportionately greatest in the smallest arteries is an early appreciation of structural, based on implied functional, differences between artery and arteriole which Ricker (415) has developed at length into a systematic neurovascular physiology.

A landmark along this way to an entirely new point of view regarding systemic vascular changes and kidney disease was the contribution of Gull and Sutton in 1872 on "arteriocapillary fibrosis" (182). As they divided their patients according to the degree of renal involvement, they were struck by the group in which the kidneys were healthy, while the heart was hypertrophied and the minute arteries and capillaries elsewhere were thickened

by "hyaline-fibroid" degeneration. "The absence of such lesions in the kidneys," they concluded, "proves that they do not constitute an essential and indispensable part of the general process. . . . . This morbid change in the arterioles and capillaries is the primary and essential condition of the morbid state called chronic Bright's disease with contracted kidney." . . . . "Though allied with senile alterations, they are probably due to distinct causes not yet ascertained." The clinical picture they drew as follows:

"A patient may come under care for headache and other allied symptoms, in whom, at a given state, the renal and cardiac functions may be normal, and as the case goes on, the urine first, or the heart first, or the breathing may first give signs of further lesion, until, as the malady progresses, that state called chronic Bright's disease with contracted kidneys may be fully produced, as shown by the thickened heart, the pale watery urine, the shrunken skin, the troubled brain, and the dimmed sight."

In 1879, Mahomed (303) presented what is essentially the modern point of view. It is significant that he had rejected the dictum that all knowledge must come from the postmortem table and had learned to use the sphygmograph with a skill that really left little to be corrected by the more accurate method of manometry. He marshalled the arguments that in lead poisoning, eclampsia, scarlet fever, he found high pressure while no symptoms of kidney failure were discoverable. Pressure was high "in some young people, in all other respects perfectly healthy, but liable to a certain class of petty ailments; such persons very often have a family history of gout or Bright's disease; and if they live long enough, will almost invariably develop it themselves." Among these premonitory signs and symptoms Mahomed listed malnutrition, cold hands and feet, palpitation on exertion, imperfect digestion, headaches and especially hemicrania, and sometimes tinnitus and diminished vision; all of which, it may be said, find a place in the present clinical picture of vasoneurosis and potential or actual hypertension. He discusses the absence of high pressure with tuberculous and amyloid kidney, and presents the statistical evidence that failure of the kidneys causes a relatively small proportion of the deaths from Bright's disease compared with lesions of heart and brain. One must agree with Ryle (434) that a great part of the story of hypertension was written at Guy's Hospital between the years of 1827 and 1881.

The frank division of opinion for and against the renal genesis of hypertension with which the first half century after Bright ended, resulted during succeeding decades in an unparallelled "grinding and rubbing at Nature." The results Janeway summed up in 1913 when he stated (225) that the "symptom of hypertension" could arise, in his opinion, in three ways.

1. "Through purely quantitative reduction of kidney substance below the factor of safety. It is difficult to conceive of this as other than a vascular hypertonus due to retained poisons of some kind." For example, bilateral ureteral obstruction and surgical removal of the only remaining kidney.

2. "In connection with the unknown intoxication which causes disturbances of the central nervous system and which we call uremia. This intoxication is not one of retention, in the strict sense." Associated with severe acute nephritis and subacute and chronic inflammations of the kidneys.

3. "In primary irritability of the vasoconstricting mechanism from unknown, probably extrarenal causes, which lead eventually to arteriolar sclerosis. In this type the disease in the kidney is the sequence, not the cause, of the generalized vascular lesion. When it progresses to a condition of extreme atrophy, resulting in the true primary contracted kidney, a renal element may be added to the existing hypertension. In some cases, arteriosclerosis of the larger vessels may spread peripherally and produce a similar form of disease. In these primary vascular diseases, it is probable that eventual, widespread narrowing of the arterial stream bed in some cases produces a permanent, organic increase in peripheral resistance."

During and since the World War, more and more the tendency has been toward the view that the causes of hypertension are extrarenal. "While every permanent high blood pressure stands in close relationship to the kidney and may be either the result or the cause of renal disease" (Volhard, 1923) it is the conception of hypertension as a "general constitutional" disease (Munk, 1925) which has widened the field of observation and increased the hope of its prevention and control.

CHAPTER III

Hypertension and Renal Disease

Arteriolar resistance to blood flow is fundamental in the pathophysiology of genuine hypertension. Over the capillary bed, Tigerstedt's "nodal point" of the circulation—where metabolic exchange between blood and tissues fulfills the final common purpose of the whole vegetative system—the neuromuscular precapillary segment exercises a finely regulated control. If, as Durig points out (127), blood mass is too small by half to fill the capacity of all the vessels, and since vasoconstriction in one part of the body is easily compensated by vasodilatation elsewhere, high pressure "can only arise when the machinery of regulation is damaged or the pressor stimuli are too powerful and overcome the depressor mechanism." In other words, increase of the tone of the arteriolar musculature, or the tetanic contraction which produces vascular spasm, must be widespread to cause elevation of systemic blood pressure. Constriction limited, for example, to the vessels of the kidney, the splanchnic area or even to all extremities (267) is inadequate to bring about hypertension.

The arterioles, in the last analysis, are subject to only two sets of influences, one exerted through the sympathetic nervous system, the other a direct effect on the vessel wall. Every agent which is to come under scrutiny as a cause of high pressure must demonstrate its pressor action through the production of central or peripheral stimulation, or both.

The first diseases to be linked with the problem of hypertension were those of the kidney. In particular, the "granular contracted kidney" was at once associated with widespread vascular lesions, and later, with heightened arterial pressure; while at the same time it was recognized that other forms of renal lesion, apparently equally destructive of glomeruli and tubules —the lardaceous or amyloid kidney is the type—were accompanied neither by cardiovascular change nor rise in blood pressure. It became evident also that height of blood pressure bears no constant relation to extent of renal damage. One or the other, indeed, may be entirely lacking (44, 329). In the range of his facts, the pathological anatomist arrived, somewhat tardily, at the point of view of the clinician, to whom as a commonplace the course of his patient reveals the sequence of hypertension, arteriolar and arterial disease, cardiac hypertrophy, and no evidence, until late in the course of events, of failing kidney function.

To a generation like the present which has been trained in the atmosphere of functional diagnosis, it is a little difficult to appreciate the authority which pathological anatomy carried in the middle of the nineteenth century. Some of the spirit and attitude of mind of that day is brought back by the chapter on "German Medicine" in Knud Faber's *Nosography*.

"Virchow maintained," he writes, "that the function of clinical medicine was to raise questions, pathological physiology to answer them. . . . . The former [medicine] lost that veneration for its own problems which is so necessary, and it then became in a great measure reduced to a kind of accessory science subordinate to pathology and physiology."

Thus the value attached in the beginning to clinical observations of blood pressure was underprized, in comparison with that credited to the study of morbid anatomy. Addis (5), deploring the wandering from the "royal road of Bright and Bartels into a maze of speculation concerning renal function" from which Volhard and Fahr have found the way back, writes: "It is when we handle the disorganized tissue, when we see the distorted cells, or by the aid of weights and measures discover the disorientation of molecular structure that we make one step which we surely need never retrace on the long way toward any real understanding of a disease entity."

But does structural pathology, at its best, do more than reveal the consequences, the after effects of heightened blood pressure? For example, as we shall see it in acute paroxysmal hypertension, of which the nature is surely functional and "prestructural?" The Romberg school (188), among others, long insisted that every permanent hypertension (over 160 mm.) is accompanied by renal changes and has defended the hypothesis that kidney disease brings the high pressure. This emphasis on the kidney as the cause of hypertension, largely explains the continued search, by all manner of tests, for signs of renal disease and disturbance of renal function. Yet experimental physiology from Bradford's day has shown how great a portion of the kidney (as much as 80 per cent) must be destroyed before its factors of safety are eliminated and insufficiency ensues. Clinical observation, too, shows conclusively that the state of the patient and his prospects are often more readily disclosed by studying the progress of the disease in his vascular system; for example, by the simple examination of the retinal arterioles.

Nevertheless, the study of hypertension through analysis of the diseases of the kidneys and their vascular relationships is a useful as well as historical approach. Following Volhard and Fahr (482), the division of Traube's "non-suppurative nephritis," or the older "Bright's disease" into the three groups of: (1) Nephrosis, (2) Nephritis, and (3) Nephrosclerosis, permits

reasonably sharp distinctions in respect to etiological factors and anatomic clinical correlations.

NEPHROSIS

Friedrich Müller in 1904 bestowed the name nephrosis upon a group of degenerative lesions of the kidney following various forms of intoxication, in order to set these apart from the exudative and proliferative lesions of true nephritis.

Nephrosis, in its pure form, is not associated with hypertension (239, 482). Vascular sclerosis, retinal lesions, cardiac hypertrophy are absent, though the degenerative processes may involve glomeruli as well as tubules, and passing from an acute stage to chronic, end as the nephrotic contracted kidney. Such an evolution leads Munk (353) to remark, "When one considers the histological picture of amyloid contracted kidney, and thinks of the marked retention in the case of granular contraction in spite of much less glomerular involvement, the state of affairs is difficult to understand, and a new point of view and new problems arise. . . . ."

In its etiological associations with the severe bacterial and chemical intoxications of the body—chronic suppurations and sublimate poisoning are types—and in its clinical features, nephrosis possesses the characters of a systemic disease. The marked albuminuria with abundant hyaline and granular casts entails a heavy loss of protein. When the plasma proteins fall below 5.5 per cent (Van Slyke) edema appears, often excessive and in the form of large effusions into the serous cavities. The presence of a lowered basal metabolism may be the key to the helpful use of thyroid.

In nephrosis the urine is conspicuously free from red blood cells. In half their patients Brown and Rowntree (91) found no reduction in hemoglobin and a normal blood volume (normovolemia), while in the remainder, there was lowered red cell and hemoglobin values in the presence of increased blood volume (oligocythemic hypervolemia).

In contrast with genuine hypertension, Westphal (495) found in nephrosis both a less constant hypercholesteremia and an insignificant rise in blood pressure following adrenalin.

In many important respects, therefore, nephrosis appears as the antithesis of the hypertensive state found in nephritis and renal sclerosis. And yet, curiously enough, the profound underlying physico-chemical changes—affecting body colloids, ionic equilibria, capillary permeability (265)—are capable of a sharp reversal, for the supervention of an inflammatory process in nephrosis can be followed by the development of high blood pressure and the whole clinical picture and course of nephritis (91, 482).

NEPHRITIS

The development of hypertension in the course of acute diffuse glomerular nephritis, appears, at first glance, to offer a simple explanation of the causal relations of high blood pressure. Injury to the renal tissue occurs, blood, albumin and cellular casts appear in the urine; normal excretion fails, toxic products accumulate in the blood; and like fever, hypertension might well seem to be a physiological and compensatory response. Closer analysis, however, has given support to an opposite conception.

In the study of war nephritis, in 1916, Nonnenbruch (366) described the appearance of edema and hypertension without urinary changes in a man who later developed frank nephritis and died of uremia. This recalled the observation of Riegel, in 1882 that arterial tension, as shown by the sphygmograph, became increased simultaneously with the signs of nephritis, and the view of Wertheimer, in 1894, that peripheral as well as renal vessels took part in the disease process. The opinion of Nonnenbruch that he was dealing with a general vascular disease has since been supported by clinical observation of the prenephritic rise in blood pressure, as well as the demonstration of water and chloride retention preceding nephritis (84, 255, 261, 483).

CAPILLARY CHANGES

Of especial interest, although in the main only indirectly helpful in its clinical application to the problems of hypertension, has been the study of the morphology and physiology of the capillaries. Lombard's (291) introduction of a practical clinical method for capillary microscopy in 1911 and the subsequent study of capillary blood pressure has led to extensive investigation and a large literature. (Hooker, Krogh, O. Muller, Kylin, Lewis.)

The arteriole, Hooker states (208), is "composed of endothelium and muscle and is defined as that section of the vessel which has lost its connective tissues and yet retains a muscular layer. . . . . As the arterioles subdividing become smaller, the muscular layer fades away. There is left nothing but the bare endothelial tube which constitutes the capillary."

Represented physiologically as an independent system which has its contractile elements and intrinsic innervation, the capillary bed nevertheless is influenced by hydrostatic pressure on the venous side (73, 74), is responsive to changes in blood flow and tension on the side of the arterioles and is altered by direct mechanical and chemical stimuli (192). Furthermore, it is capable of causing important reflex changes in the adjoining vessels (261).

Dale (108) among many emphasized the conception of the independence of capillary function.

Ricker (415), on the other hand, cannot recognize an independent capillary physiology and pathology. The changes which the terminal peripheral bed undergoes in health or disease are regulated by the action of the small arteries and arterioles immediately proximal to the capillaries. Looking at the arteriole as a neuromuscular organ, the play upon it of stimuli, according to their progressively increasing strength (Verworn), produce, in order, dilatation, constriction, and after constrictor paralysis, dilatation. Therefore, there may result, Ricker conceives, all possible degrees of capillary blood flow from hyperemia to stasis, and in consequence "peristatic" changes which vary all the way from simple serous transudation through hemorrhagic exudation to necrosis of the perivascular tissue.

Kylin (261) found, in 1919, that a rise in capillary pressure occurred even earlier than the elevation of arterial pressure in patients who developed nephritis after tonsillitis or scarlet fever. The rise appeared several days to a week before the changes in the urine. From the normal range of 10 to 20 mm. Hg, the capillary tension rose gradually as high as 50 mm. and in severe cases, to 70 mm. The rise in arterial pressure was commonly from 25 to 30 mm. before albuminuria appeared. In cases of severe nephritis arterial pressure bore no relation to the capillary hypertension, and in these patients it was necessary to postulate arteriolar hypertonus as a reflex effect of the capillary injury.

In benign nephrosclerosis Kylin found, in contrast, that the capillary pressure remained normal, unless congestive heart failure brought a moderate elevation, and concluded that hypertension could be divided into two distinct types, one a pure arterial hypertension, and the other in which the primary factor was diffuse inflammation of the capillaries. He suggested that the name "acute generalized capillaropathy" was a more appropriate name for the disease than nephritis. Independent observations led Munk (353) to the similar conception of a systemic capillaritis and the extrarenal character of so-called acute glomerular nephritis.

Studies by Koch (255) of scarlatinal nephritis, using Kylin's own method, have shown no change in capillary pressure, though confirming the prenephritic rise of arterial tension. Lange (266) also observed no capillary changes in the course of acute nephritis. Lundberg, cited by Kylin, has confirmed the latter's work in the clinic, and Beckmann (56) brings support from the simultaneous occurrence of capillary and arterial hypertension after adrenalin and lead and in experimental nephritis. Herzog (201) has recently reported finding the capillary tension elevated in nephrosclerosis

and normal in nephritis. Thus it is evident that criteria and methods require further standardization, but the discrepancies leave unaltered the conclusion of Kylin "that either in the capillaries or in the small arteries, or in both, pathological changes must be present to excite the abnormal conditions of blood pressure."

Since the newer evidence, on the whole, bears out the old theory that a general arterio-capillary affection underlies the syndrome of hypertension, these structural changes are brought into close relationship with the problems of infection, immunity, and allergy. In the development and course of capillaritis and nephritis there are many analogies with rheumatic fever. The occurrence of glomerular nephritis in association with polyarthritis (Stettner) and endocarditis (Baehr and Sacks); the description of vascular lesions in the kidney similar to those of rheumatic fever (Fahr, Evans); the etiological relations with tonsillitis and the streptococci; all suggest, although as Swift (467 a) points out, do not prove a common pathogenesis.

It is not without significance, perhaps, that nephritis is most likely to appear in the second and third week after the primary infection, when the patient is convalescent, and at the time when the blanching phenomenon (Charlton-Schultz) indicates the development of immunologic tissue reactions (255). While the albuminuria of the febrile stage is usually considered to be unrelated to the later nephritis, the possibility of sensitization in these patients is not beyond suspicion. Long (292) has produced acute glomerular nephritis by the injection of tuberculin in sensitized animals.

NEPHROSCLEROSIS

In its relations to arterial and arteriolar disease, and especially as these vascular disorders affect the kidney, hypertension has long been a problem to the philosophers and investigators of medicine. Naturally the close association of renal and vascular changes has always suggested a pathogenetic unity. The discussion has concerned which was cause and which effect. Sir George Johnson (229) was one of the first, Harpuder (188) of the Romberg school one of the last, to support whole-heartedly the primary importance of the kidney. The rôle of structural changes in the terminal vascular bed—the arterio-capillary fibrosis of Gull and Sutton—may be granted a place, if only secondary, in maintaining hypertension. But general recognition has been given to the high pressure as the primary disturbance, one which is no more the result of arteriosclerosis than the indisputably secondary cardiac hypertrophy.

On purely hemodynamic grounds it is agreed that narrowing of the renal vasculature is insufficient to produce a systemic rise in blood pressure.

Proof of chemical and nervous reflex factors that might possibly originate in the kidney has not been adequate. Of sclerosis in other areas, for instance, of the splanchnic vessels (87), and of generalized arteriosclerosis, it has been shown, a minority dissenting (347, 433), that the process is never so severe or extensive (127, 154) that anatomical disproportion between blood volume and the capacity of the vessels is at all likely to give rise to permanent high pressure. The almost unanimous opinion of a preceding generation that permanent hypertension could be traced to underlying structural disease in kidney or blood vessels has yielded to a wider and more fruitful pathophysiology.

If vascular disease in the kidney is presented not as the cause, but as the result, and almost a synonym of permanent hypertension, the assumption that "wear and tear" of the vessels is the predominant factor must face the opposition of those who emphasize agents other than blood pressure. MacCallum (295) analyzed the causes of arteriosclerosis, grouping them as mechanical, toxic, and dietary, and concluded that heightened blood pressure alone produces little or no change in the arteries. In a pathological and clinical study of arteriosclerosis in relation to kidney disease, Evans (135) stated that a persistent systolic pressure of 190 mm. Hg or over, is evidence of diffuse hyperplastic sclerosis and its clinical expression. He regards these arterial changes—intimal thickening and degeneration in the vessel wall—and the allied chronic renal disease, as the result of active inflammation caused by a common and simultaneously acting, though unexplained, pathogenetic factor. Foster (160) has surveyed the clinical and experimental facts regarding vascular sclerosis and "nephritis of the vascular type" and could find no adequate evidence for belief that hypertension is a predominant factor in the causation of arteriosclerosis. Rather, in his opinion, do the intoxications, arising from infections and abnormal metabolism from which few lives are free, bring about "functional disorders chiefly referable to the nervous system" and if persistent, structural changes affecting the blood vessels and kidneys. For the scars of arterial degeneration, Foster says, the whole blame should not be placed on vascular strain without the strongest evidence in support. Infections are also emphasized by Ophüls (381), Post and Stieglitz (408) and Barach (45).

Can evidence of vascular strain be brought?

Apart from the fact that infection, both acute and chronic, has so often a directly hypotensive effect (79, 483, 495), the lack of parallelism between arteriosclerosis and hypertension, even in the face of known degenerative factors, suggests at once that the causation and evolution of the two conditions are not the same.

Persons in health, or those who come to the physician with the symptoms of the common disorders of adult life not especially related to blood pressure, frequently enough have mild hypertension. Their blood pressure is persistently above 140 mm. Hg systolic and 90 mm. diastolic, as early as the second and third decades of life, without the slightest evidence of structural vascular disease. Fluctuating and intermittent at the onset, as years pass the blood pressure in these patients becomes higher and more constant, and the cardiac hypertrophy, aortic dilatation, thickening of the accessible arteries and the smaller vessel changes made visible by the ophthalmoscope or capillary miscroscope reveal the general vascular disease.

"Whoever has witnessed how in many of these patients the high pressure appears from a mass of nervous ills as the first tangible symptom of disease; how this symptom, at first so variable and inconstant, by gradations becomes stabilized; whoever sees the first signs of retinal and renal lesions appear and progress as the patient returns again and again in the course of the years, he will be hard to convince that there is not at work here an orderly pathogenetic sequence from functional to organic vascular disease" (Otfried Müller (352)).

Fahrion's (146) statistics from the Tübingen clinic show that height of blood pressure and evidence of kidney disease go hand in hand. In 1763 patients, 53.8 per cent were free from signs of renal impairment when the blood pressure was at the 140 to 159 mm. level. At 160 to 199 mm., 39.4 per cent., and at 200 mm. or above, only 15.7 per cent had normal kidney findings. The percentage of impaired renal function was greater in diabetes mellitus than in adiposity, and the innersecretory influence of the menopause was least marked.

The clinical picture of the evolution of hypertension is supported by physiological and anatomical distinctions between arterial and arteriolar disease (33). A corollary is the separation of nephrosclerosis, the primary contracted arteriolosclerotic kidney, both from the senile arteriosclerotic kidney on one hand, and on the other, the true nephritis of bacterial and bacterio-toxic origin.

Hypertrophy of the arteriolar muscle as evidence of contractile activity is found conspicuously present in cases of severe, rapidly progressing hypertension (243). Such examples are best seen in malignant hypertension and in acute nephritis; in long standing hypertension, the hypertrophic changes in the media are replaced by degeneration and atrophy (154, 155).

Convincing proof of the effect of vascular strain is the rapid development of hard tortuous arteries reported in severe glomerulonephritis by Moschcowitz; (341) with the subsidence of blood pressure, the vessels

again became soft and impalpable. That the arterial change was not wholly due to the increased tension was shown in one case by the anatomic finding of a thickened muscular layer in the absence of intimal thickening, cellular infiltration or necrosis.

Equally significant of the distinctive hypertrophic nature of hypertensive vascular disease in contrast with degenerative senile arteriosclerosis are the diffuse vascular changes described by Keith (242) and his co-workers in malignant hypertension. "The changes in the arterioles are different from those observed in the arteries of old persons: there is more marked hyperplasia of the intima and hypertrophy of the media and internal elastic lamina, in contrast with the degenerative changes in senile arteriosclerosis with their deposits of lipoids, fatty acid and calcium in the intima, and fragmentation, but little hypertrophy, of the internal elastic membrane. Again, in senile arteriosclerosis the smaller arteries and arterioles do not manifest the extensive intimal hyperplasia and the marked narrowing of the lumina." Their experience leads Keith and his associates to consider the hypertension primary and hypertrophy of the arteriolar wall the result of excessive strain and activity, though they consider further study of the early stages of the disease necessary to decide the question.

Aschoff (33) has expressed the view that hypertonia, whether primary or secondary, never leads to an atheromatosis, but to a true hypertrophy of the entire aortic system with involvement of all the coats, while the real atheromatosis of the aorta is primarily a disease of the intima. As an example of this latter type of infectious origin, there come to mind the discrete spots of intimal hyperplasia of the aorta seen during the world war in previously healthy young soldiers who died of pneumonia.

From their pathological study of 420 cases of primary hypertension, Bell and Clawson (57) came to the conclusion that "renal arteriolosclerosis seldom if ever occurs in cases in which hypertension can be definitely excluded." The anatomic changes in the kidney of hypertension were of all degrees, but in 75 per cent of their series, there was no evidence of infection. There was never a true arteritis, and the character of the renal lesion changed only when acute uremia developed and anatomically a complete and rapid occlusion of the afferent vessels resulted in mural necrosis and glomerular infarction. This was the picture of "severe acute arteriolosclerosis." As a terminal infection, glomerulonephritis was sometimes seen, and in chronic uremia there was ischemic atrophy from progressive arterial or arteriolar narrowing. And while Hueck (216), and Munk (353) have maintained that the hyaline intimal deposits produce no increase in resistances to blood flow, it is the view of Bell and Clawson that

such changes must narrow the lumen as well as interfere with normal vascular relaxation and contraction, and therefore play a part in the maintenance of high pressure.

The histological difficulties which arise in differentiating vascular from inflammatory renal lesions are brought out by Fishberg's (154, 155) studies of the anatomic findings in nephritis and hypertension. In a number of patients with severe acute diffuse glomerulonephritis, acute necrotizing arteritis was found in the absence of hypertension and consequent vascular strain, could be regarded as purely toxic in origin. Yet such lesions are similar to those described by Bell and Clawson and first given by Fahr the name of malignant sclerosis, though it is clear that they are no longer to be explained as a "combination form" of toxic-inflammatory component plus vascular disease. Hartman (189) and later O'Hare (376) with their co-workers, have shown the difficulty of differentiating the renal lesions produced by Roentgen radiation from those of true nephritis.

Arteriolosclerosis of the same histological type and distribution as found in chronic hypertension was present in all Fishberg's cases of prolonged nephritis. Hypertrophy of the muscular layer was not found in early cases of chronic nephritis, was well marked in many cases of considerable duration, even in the absence of great intimal thickening, and had been replaced by atrophy in the oldest cases.

The development of arteriolar changes of such striking similarity in two dissimilar types of disease must be considered strong evidence that they are the result of the one common factor, hypertension.

"Neither the so-called parenchymatous or non-indurative, nor the so-called interstitial, indurative form of kidney disease, represents a pathologic entity," wrote Volhard and Fahr in 1914. "The criteria for the division were primarily blood pressure and renal function. We found under the parenchymatous-hydropic disease two main forms set apart only by the rise of blood pressure; in the interstitial syndrome of high blood pressure two chief types separated only through renal function."

And since they concluded further that blood pressure elevation, "seems, apart from anuria, to depend principally on the diffuse involvement of the renal vessels," thus arose the concept of benign and malignant sclerosis of the kidney. For the severity of the malignant form, retention of spasm-producing substances was made responsible by Hülse, supported by Volhard, in 1923 (217, 483).

In 1924 Wagener and Keith (484) reported a series of cases which had been referred with the diagnosis of chronic diffuse glomerular nephritis, but renal function was normal or little impaired, and anemia was absent. The history

and clinical findings differed from those of nephritis, and the persistent marked hypertension, adequate renal function, and severe neuroretinitis, seemed to constitute an entity which they called malignant hypertension. Death occurred in all these patients within from one to forty-four months after coming under observation. In a series of papers Keith and his associates have described in detail the clinical picture and course, necropsy findings, and most recently, the diffuse arteriolar changes which are revealed in the pectoral muscle obtained by biopsy.

In 1927, Keith (241) summarized the findings in 81 cases of malignant hypertension. Duration of symptoms had been from one month to six years. Visual disturbances o curred in 43, dysmea on exertion or edema in 49. Peripheral arteriosclerosis in some degree and neuroretinitis were present in all. No anemia was found in any patient, marked cardiac decompensation was found in 9 cases, marked renal insufficiency in 7. The systolic pressure ranged between 280 and 190, the diastolic pressure between 200 and 120. The Wassermann test was negative in 74. There were 73 patients (90 per cent) who died within fifty-one months. The average length of life after the diagnosis was made was eight months. Only 5 patients lived two years or longer.

In 7 necropsies, Kernohan found that the heart was always hypertrophied, although the degree varied with the duration of the history of hypertension. Sclerosis of the coronary arteries and aorta was moderate. The kidneys usually weighed little less than normal, and the severe histological changes were vascular and not inflammatory. There was diffuse arteriolar disturbance with hypertrophy of the media and intimal proliferation.

Keith suggested the clinical classification of (1) benign, (2) severe benign, and (3) malignant hypertension, because of its value in diagnosis and prognosis. There is evidence that the basic lesion in the three groups is one of degree, but on the other hand, in the great majority of cases of benign hypertension the malignant syndrome never develops.

Rosenthal (428) was unable to separate benign from malignant forms of arteriolosclerotic kidney, and P. Klemperer and Otani oppose this division (254).

CHAPTER IV

The Functional Basis of Hypertension

In spite of the high and variable ranges of arterial pressure which are found in permanent hypertension, it is striking that the pressure in the capillaries is almost always normal or, frequently, subnormal. This reduction of a systemic pressure of 200 mm. Hg in the brachial artery to one of 20 mm. or less in the finger capillaries, with obliteration at the same time of the pulse pressure, is necessarily accomplished in the arterioles. Such arteriolar "throttling," Landerer (264) concluded, is more important in regulating capillary circulation than the actual arterial pressure, for it is the resistance in the terminal vascular bed which not only reduces high to low tension but converts the intermittent, pulsating arterial flow into an even, continuous capillary current. Without such a transforming mechanism, the interesting suggestion is made by Nesterow (356) that periodic failure of tissue nutrition between pulse beats might well lead to distinct rhythm, in thought, seeing and hearing. As a matter of observation, a true microscopically visible capillary pulse is rare even in aortic insufficiency.

How far to the periphery—even in the arteriolar limb of the capillary loop—this constriction and resistance may lie, Heimberger (192) has shown by demonstrating a true pulse in one capillary, while in its neighbors, springing from the same arteriole, pulsation was absent. Stimulation of various sorts in the precapillary area also was capable of producing capillary pulsation. Spastic contraction of the arteriolar capillary limb, lasting many minutes, was found by Westphal (495) as a characteristic reaction of hypertensive patients after compression of the brachial artery. Lange (267) has contrasted this evidence of abnormal vasomotor response in pure hypertension with the depression of sensitiveness in arteriosclerosis.

A study of capillary morphology and function in hypertension by Müller and Hübener (352) carries facts and conclusions of weight and fundamental importance. In fifty cases of pure hypertension renal insufficiency was rigorously excluded by demonstrating absence of nitrogen retention in the blood, normal capacity of dilution and concentration of urine, and normal excretion of sodium chloride and urea. Cardiac insufficiency was ruled out. In these hypertensive patients, compared with the orderly disposition of the peripheral vessels found in healthy persons, there was present

complete irregularity and lack of pattern in the architecture of arterioles, capillaries and venules. The abnormally contracted arteriolar limb and the pathologically dilated venous limb gave a characteristic "spastic-atonic symptom complex." The venous congestion, involving the subpapillary plexus as well as the superficial vessels, offered an obvious physiological explanation of the "red" hypertension of Huchard (215) and Volhard (483). Capillary flow was irregular, stasis was frequent, and the coiled and contracted loops suggested glomeruli. In contrast, patients with the secondary contracted kidney of chronic nephritis and blood pressure equally high, had capillaries arranged in orderly fashion, with no disproportion between arteriolar and venous segments and without glomerulus like appearance. The capillaries were somewhat contracted, especially on the arterial side and the picture could be called the "spastic symptom complex." The subpapillary plexus was barely visible and here was the basis for "white" hypertension. In both forms of hypertension, capillary pressure was normal or below normal. In pure hypertension, authors conclude that evidence of kidney disease is entirely lacking, and there are unmistakable signs of constitutional vasoneurosis. In the second group, the high pressure is the result of acquired (exogenous) general vascular or renal disease, and the signs of inherent abnormality of the peripheral vascular system are not found.

The conception of vasoneurosis embraces the vascular disturbances related to the disorders of the "vegetative system" of Friedrich Kraus (259, 260), the chief components of which are the sympathetic nervous system, the electrolytes of the body tissues (notably, the calcium and potassium ions) and the endocrines. Since the soil for vasoneurosis is contained in the germ plasm—Müller and Hübener cite the contrasting characteristics of single and double ovum twins—the influence of heredity becomes of primary importance. Numerous clinical studies give abundant support (45, 335, 374, 427, 491). Since the morphological, though preclinical signs of vasoneurosis are common, the search for the factors which prevent or precipitate hypertension in one patient, ulcer of the stomach in another (281), glaucoma in a third (352), render the study of constitution and environment of no less moment. The clinical fellowship which hypertension appears to betray for gout, diabetes, obesity, suprarenal hyperfunction, and its dissociation from asthma, pulmonary tuberculosis and suprarenal insufficiency bring wide problems in the field of practical medicine. The study of the functional and anatomic substrata of high blood pressure becomes a major problem of biology (492).

As a guide in analyzing hypertension, the classification of Kahler (235)

has at least the merit of a systematic scheme. Recognizing its essential unity as a disorder of vasomotor regulation, Kahler divides hypertension into functional and anatomic. Functional hypertension is caused by arteriolar hypertonus and contraction; anatomic hypertension depends on structural arteriolar narrowing. It is the contrast between Volhard's angiospasm and angiopathy (483). The first is reversible, the second is fixed. Since the organic changes are the aftermath and always combined in greater or less degree, with the functional, it is the primary and basic disorder which demands chief consideration.

A classification of hypertension (after Kahler)

A. Functional hypertension.
Increased tonus or contraction of arteriolar musculature caused by:
I. Central stimulation (vasomotor center).
1. Primary.
a. Psychic.
b. Mechanical (increased intracranial pressure).
c. Lesional (brain injuries, localized vascular disease).
d. Toxic (chemical pressor substances).
2. Secondary (reflex effects, e.g., from visceral pain).
II. Peripheral.
1. Primary (direct toxic action, e.g., adrenalin, guanidine).
2. Secondary (reflex effects, e.g., from capillary injury in nephritis).

B. Anatomic hypertension. General or extensive structural narrowing of the arterioles. The result of, and usually combined with, functional hypertension.

(The systolic elevation of blood pressure resulting from increased cardiac output, e.g., in aortic insufficiency or thyrotoxicosis, is not included as a part of genuine hypertension)

According to their origin, the stimuli which cause functional arteriolar change fall into two groups: central and peripheral. The central stimuli, acting on the vasomotor center, include (a) psychic disturbances; (b) increased cerebral pressure; (c) inflammatory and vascular lesions and (d) toxic substances. In the periphery, constrictor substances, of which adrenalin and guanadin are examples, act directly on the arteriole. Secondary reflex stimulation also may occur, for example, from the damaged capillaries in the syndrome of "nephritis." Severe visceral pain constitutes a peripheral factor which has a secondary central action. Kahler's clinical differentiation, based on the blood pressure response to the withdrawal of spinal fluid, venesection, and the effect of caffeine and other drugs on the centers, is of great interest, though obviously the procedures and the classification have their difficulties of application in everyday practice.

PSYCHIC FACTORS IN HYPERTENSION

Lability of blood pressure is a biological asset. An effective pressor response to an adequate stimulus is to be considered physiological evidence of a well-balanced vegetative system, and necessary in the face of emergency, for physical efficiency and even maintenance of life. But when the emergencies become too frequent, or when slight and insignificant stimuli

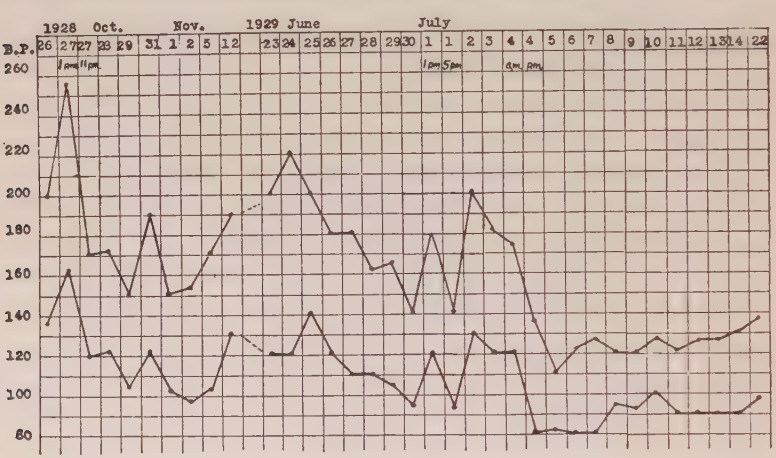

FIG. 1. THE VARIABILITY OF BLOOD PRESSURE

A man, aged fifty-six years, a manager, with chronic hypertensions of ten years standing, was seen after a digestive upset. A severe occipitofrontal headache prevented sleep. Withdrawal of 10 cc. of clear spinal fluid reduced its pressure from 18 to 5 mm. The blood pressure (October 26) from 200/138 to 210/140 and later 240/140, and on October 27 to 256/162. After three doses of sodium bromide-chloral hydrate (of each 15 grains), in ten hours the pressure fell to 170/120. With rest the blood pressure remained low, but rose again on return to work.

In June, a bronchitis was followed by otitis and mastoiditis with operation on July 1. On July 4, signs of brain abscess appeared, with fever (102°–103°F.), pulse 100. Respirations 20–24. Optic neuritis developed. Despite the fall in blood pressure, blood chemistry on July 8 showed sugar 95, nonprotein nitrogen 31, creatinin 1.6, uric acid 2.2, chlorides 410. Gradual recovery, without operation, took place. The patient returned to part-time work in September, with a gradual rise in blood pressure to its former level of 170–180 mm. I am indebted to Dr. Nicholas A. Mandelos for the blood pressure records during the period of infection.

fall upon the susceptible system of the vasoneurotic, the conditions are provided whereby eventually a continuous flow of psychic disturbances brings a permanent rise in blood pressure.

Perhaps the first practical lesson in the study of hypertension is to evaluate in patients the effect of mental and emotional stress. Often it is a much more important element than physical strain. The nervousness and

apprehension at physical examination, disquieting news and painful thoughts, elation or chagrin over a hole in golf, an irritating and discordant radio next door, serve to illustrate influences in raising blood pressure so definite that by the responses they call forth light is thrown simultaneously on the nature of the patient and his disease, and the proper management of both.

The experience of races as well as of persons reveals the importance of the psychic factor in hypertension. In the African negro tribes of the Kenya

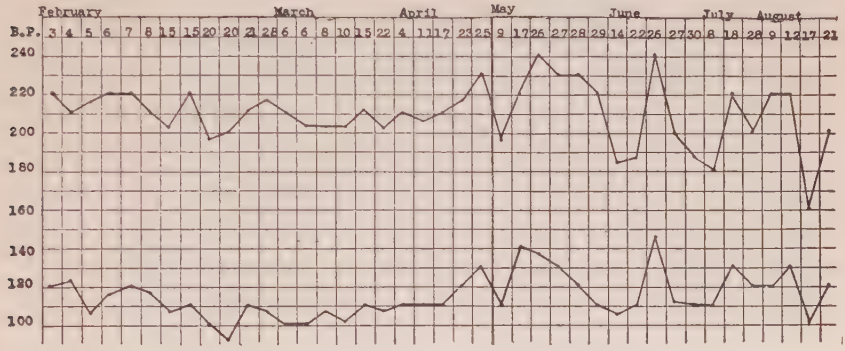

FIG. 2. THE FIXATION OF BLOOD PRESSURE

A man, aged forty-nine years, an executive, with hypertension of seven years' duration, had a cerebral "stroke" on February 3, a second on May 26, a third on June 26. He died on August 21, with the picture of low-grade uremia. Pyuria had been present during the last three months of life, but urea nitrogen two days before death was 17. Lack of response to treatment is outstanding. Terminal weakness may be held responsible for the final variation. Withdrawal of spinal fluid relieved coma, Cheyne-Stokes' breathing and papilledema, but did not reduce blood pressure. On February 15, the blood pressure was 204/108 before, 220/110 after, removal of 35 cc. of spinal fluid. On February 20, 500 cc. of blood were withdrawn; the pressure was 196/100 before, 200/90 after venesection. Response to drugs was also lacking. A pulse rate of 100 to 120 was almost constantly maintained for six months! Seven years previously, severe retinitis had disappeared under treatment, and although arteriolar changes were pronounced, exudation came only in the last two months of life!

Colony, lying in the Lake Victoria Nyanza region, almost uninfluenced by civilization, Donnison (116) reports 1800 admissions to the mission hospital without a single case of hypertension. In a study of 1000 healthy men, he excluded the first reading on account of the effect of nervousness, for a temporary pressure of 200 mm. was not infrequent. But in only one person did such a rise persist as long as two hours. In these negroes cardiac hypertrophy was rare and arteriosclerosis was late in making its appearance, usually not until after fifty years, and then mild in degree. Infections, nevertheless, were extremely frequent. Pyorrhea was universal in

adults over thirty years. Tonsillitis, chronic skin ulcers and constipation prevail in the "blacks" and meat is a large element in the diet. It is the lack of a tense existence which is an outstanding feature of the tribal life.

In Egyptians, Ismail (220) found that hypertension was rare in hospital practice there confined to the lower laboring classes. Infections were common. In the private clinics, attended by the middle and upper classes, largely brain workers, 10 per cent were hypertensive. By the majority of these people alcohol had never been tasted. Coffee was consumed in equal quantity—even to the extent of 40 cups a day—by hypotensive and hypertensive patients alike. Social position, or the expenditure of the energy required to maintain it, therefore, was regarded as an important hypertensive factor, coupled also with heredity and excess of protein food.

In China high blood pressure is a rare finding. Among 4000 patients in the medical wards at Changsha, J. H. Foster (158) found one instance of essential hypertension. This was the case of a Chinese nurse, a highly nervous woman, who had gone to America to finish her education and had returned with the habits and attitudes of a "Westerner." Including the patients with heart and kidney disease, not more than 20 persons showed a blood pressure above 160 mm. Hg.

This incidence is compared by Foster with the percentage of 4.6 for hypertension in Boston patients at Peter Bent Brigham Hospital.

The average systolic pressure for the group of Occidentals was found lower in China than it had been in America. It was below the American average and approximately the same as that of the natives. Tung reported similar findings (474). While exceptions occur, and certain observations, cited by Foster, of the blood pressure of the white races in China, the Philippines and India, show little departure from the average at home, hypertension is conspicuous by its rarity. Factors of constitution, of diet, and of climate seem, on analysis, relatively unimportant (95), and the impression is left that it is the unhurried life of the East, the "Old Philosopher's" acceptance of fate, permeating the civilization and people of China, which offers the great contrast with the Western arena of stress and hypertension.

In the tropics Roddis and Cooper (419) found that the blood pressure of white men was 10 to 15 mm. lower than in the temperate zone, due, it appeared, to decreased vasomotor tone along with a general slowing of physiological activity.

The often unappreciated influence of psychic factors is exerted strongly for better or for worse, in the earler years of life. The circulatory apparatus takes its fair share in the responses which guide the mechanism of character

TABLE 2

Hypertension in the thin, normal and obese (an analysis of the weight and blood pressure of 3397 patients)

AGE	THIN			NORMAL			OBESE		
	Total number	Per cent with blood pressure		Total number	Per cent with blood pressure		Total number	Per cent with blood pressure	
		140 mm.	150 mm. (and above)		140 mm.	150 mm. (and above)		140 mm.	150 mm. (and above)
Men									
Under 20	10	0.0	0.0	26	0.0	0.0	5	0.0	0.0
20–29	75	10.6	1.3	153	10.4	5.8	46	23.9	10.8
30–39	145	9.6	6.2	153	7.84	2.6	69	21.7	8.7
40–49	125	20.0	12.0	153	24.1	12.4	70	34.2	14.2
50–59	87	24.1	14.9	127	37.0	28.3	86	60.4	40.6
60–69	53	50.9	32.0	85	68.2	55.3	63	73.0	65.0
Total....	495	19.1	11.1	697	24.4	16.4	339	43.6	28.3
Women									
Under 20	26	7.7	0.0	33	0.0	0.0	15	0.0	0.0
20–29	142	2.8	2.1	127	4.7	1.6	77	6.5	1.3
30–39	118	6.7	0.8	152	9.2	1.9	118	27.1	11.8
40–49	100	27.0	19.0	120	30.0	18.3	176	48.2	30.7
50–59	85	43.4	25.8	157	63.6	47.7	214	66.7	50.4
60–69	36	47.2	33.3	74	62.1	50.0	96	72.9	51.0
Total....	507	18.7	11.2	663	31.0	21.7	696	48.0	32.4

Table 2 has been prepared from data obtained in the department of medicine, Cornell Clinic with the assistance of Dr. Ralph G. Hurlin, the Russell Sage Foundation, New York City. The mathematical and statistical presentation, however, is reserved, as Dr. Hurlin has noted that the groups are small and that the pressure distributions are skewed, particularly for the older age groups.

The author offers the present data in the form of percentages as confirmatory of: (1) the incidence of hypertension in unselected medical patients; (2) his experience that the sexes exhibit little difference in the extent to which each is subject to high blood pressure; (3) the progressive increase in elevated arterial tension with age; and (4) a highly suggestive preponderance of abnormal blood pressure in the heavier patients.

As the standards for normal weight, there were taken the average height-weight-age figures and variations up to 10 per cent above and below.

formation. In schoolboys who were under strict discipline Stocks and Karn (463) found a greater average systolic and pulse pressure than in boys in easy going schools, but the pulse rate decreased in compensation. Regular physical exercise, they noted, tended to keep the diastolic pressure at a lower level, presumably by reducing peripheral resistance, whereas a sedentary mode of life tends to raise it, the systolic pressure being similarly but less affected.

In modern college life and even in the preparatory schools, often the same though self-imposed discipline is brought into being by the spirit of stress and competition.

In a study of 630 English school children, Lord Dawson of Penn (110) found 8 per cent with pressures over 130 mm., and in classes just prior to examinations an incidence above this level of blood pressure which was two and one-half times that for the school as a whole. His opinion is that "a rise in pressure occurs normally in anticipation of effort, and anticipation—the desire to forestall—plays in civilization an increasing part which shows reactions with bodies and minds of a certain physiological cast."

Moschowitz (342) believes that the "states associated with hypertension are essentially by-products of the struggle for existence, the ultimate consequences of the strenuous life"—in opposition to Bowers (80) who failed to find a psychic factor. After giving the patient some insight into the nature of his disease, and providing for reduction of diet, Moschowitz seeks to develop ability to play and relax in order to husband energies prematurely exhausted at middle age.

In 500 soldiers of the German Army, in 1917, Stahl (454a) found a pressure of 160 to 190 mm. in 30 per cent and of 200 mm. or more in 5 per cent. The exposure of the field and its mental and physical strain of campaigning seemed to be important factors. In Otfried Müller's patient a blood pressure of 280 mm. persisted for two months, with pulmonary edema albuminuria and oliguria until it was discovered that he was worried about affairs at home and separation from his wife. After she visited him, his blood pressure fell to 150 mm., his urinary excretion became normal and he made a speedy recovery. Several years later his systolic blood pressure was 130 mm.

CEREBRAL CIRCULATION AND HYPERTENSION

The interdependence of general and cerebral circulation is an observation as old as historical medicine. It was shown, if not fully understood, in the demonstration of syncope following pressure on the carotid (το κάρος, sleep) and is newly confirmed by the "crossed circulation" experiments of modern physiology. François Franck showed that increased intravascular pressure

in the brain was accompanied by a fall in arterial pressure elsewhere, and Cushing proved that increased intracranial pressure caused a rise in systemic arterial tension sufficient to overcome this pressure and maintain medullary circulation. By supplying the brain of one dog with blood from the "heart-lung preparation" in a second animal independently of the first animal's general circulation, Anrep and Starling (28) found that "changes of the blood pressure of the vasomotor center produce the reverse changes of the blood pressure in the rest of the body." That the mechanism could be exclusively central, was shown by the lack of effect of cutting the vagi. The reciprocal blood pressure changes continued as long as the conditions of cerebral flow and pressure were maintained; they were abolished by section of the spinal cord.

Making clinical application of these facts, Starling (457) has said that "no pathology of hypertension will be adequate which does not take into account the sensitiveness of the vasomotor center to the changes in circulation through it which determine the height at which the arterial pressure is set."

In order to establish the anatomic basis, if present, for impaired medullary circulation as a pathogenetic factor in hypertension, Bordley and Baker (78) selected 24 cases of generalized arteriosclerosis in which there had been adequate clinical and pathological study. Transverse sections were taken from the medulla in the area ("lateral to and above the obex") where Ranson and Billingsley had demonstrated, by electrical stimulation, pressor and depressor points. Arteriosclerosis was found uniformly in the 14 cases in which chronic hypertension had existed, (in 8 death was from cerebral hemorrhage) and was absent in the 10 without a hypertensive history. In the small arterioles the media was found in some cases "extraordinarily thickened." The larger vessels were more likely to show intimal changes. The alterations, however, were not accepted as hypertrophy, but as "the end stage of some slowly progressing necrotic process." Hypertension was considered as the compensatory mechanism to prevent bulbar anemia.

After studying the histology and distribution of the arteries of pons and medulla in over 40 unselected control cases, Cutler (107) continued his investigation in 18 cases of hypertension. In 10 of these, he found no arteriolar thickening, in 4 slight changes, in 4 changes of, at most, moderate severity. The most marked sclerosis was in patients who had died of cerebral hemorrhage and whose blood pressure had been over 200 mm. Hg. There was no case of arteriolosclerosis, however, without hypertension, though in the large arteries sclerotic changes were present in 10 patients without hypertension. There were no gross changes in the injected specimens to show that the anatomic lesions present interfered with the blood supply.

Lange (267) has also carried out most careful histological studies of the brains of arteriolosclerotic patients and found no definite tissue changes.

From the clinician's point of view, it can be said that the conception of permanent hypertension as the result of functional or anatomic changes in the vasomotor center is attractive, but not easily accepted. It is perfectly adapted to explain paroxysmal dyspnea, the respiratory arrhythmias of Cheyne-Stokes and of Biot, and the hypertension of stasis (Sahli's *Hochdruckstauung*) in congestive heart failure or left ventricular insufficiency. But in uncomplicated chronic hypertension the theory demands the selective stimulation of one center, without affecting its neighbors. And, if an organic narrowing of the medullary arterioles is accepted as the important factor, it again is difficult to explain the wide variations in blood pressure in these patients. Something more potent than anemia alone, it is admitted, must be thought of, for in profound anemia there is no evidence of abnormal activity of the vasomotor center. Perhaps the most inacceptable part of the theory of primary medullary vascular disease to the clinician is its contradiction of the facts which are disclosed, for example, by the retinal arterioles—so closely related to the cerebral vessels (150, 332)—of the evolution of hypertension by way of primary functional disorder.

Other lesions which may affect the medullary centers directly or indirectly—injuries, hemorrhage, either traumatic or secondary to arterial disease, brain tumor, such inflammations as encephalitis or brain abscess—are unimportant or infrequent in the causation of chronic hypertension. Acute elevation of blood pressure as in fracture of the skull or apoplexy is usually accompanied by signs of manifest or latent cerebral pressure—slow pulse, headache, vomiting, papilledema. Under such circumstances, lumbar puncture employed with caution and preferably under manometric control often is found exceedingly helpful in diagnosis and treatment.

The importance of brain tumor as a cause of hypertension has been exaggerated. In 44 cases Hench (cited by Keith) found only 2 patients in whom the blood pressure was elevated. Amberg (25) reported hypertension in a boy with temporal lobe abscess; surgical drainage brought complete relief of both conditions.

Paroxysmal hypertension in the course of subacute meningococcus meningitis has been reported by Weber (487). His patient was a woman, aged twenty-eight years, whose blood pressure during the crises rose from 135 to 224 mm. There was bilateral papillitis. At necropsy internal hydrocephalus was found. The suprarenals were normal. A primary irritation of the vasomotor center appeared probable.

Mühlmann (347) believes that liposiderosis of the brain capillaries pro-

duces hypertonus. Liposiderin is the union of lipoid with iron derived from broken down red blood cells. Its deposition, he assumes, brings anatomical hindrance to cerebral circulation and augments a "physiological" hypertension, which he thinks arises under normal conditions of growth, increase of blood volume outstripping the capacity of the vessels to contain the blood mass.

Antoine (29) has described a case of cerebrally conditioned unilateral loss of pulse involving left arm and leg, ascribed to simple spastic contraction of the vessels.

Irritation of the vasomotor center and high pressure following electrical shock was reported by Pfalz (400). Experimental stimulation of the brain center has brought variable results (475).

The acute cerebral episodes of diffuse glomerulonephritis, eclampsia and lead poisoning have been given a full review by Oppenheimer and Fishberg (383). The clinical features and the pathophysiological evidence indicate strongly that this hypertensive encephalopathy is the result of cerebral anemia produced by vasoconstriction.

In 250 readings of arterial and cerebrospinal fluid pressures, Claude and Lamache (101) found no constant relation between the two. Of 47 hypertensive patients, 7 had cerebrospinal fluid pressure of 25 mm. or more. One patient with a pressure of 45 mm. and papilledema had a blood pressure of 260/140; at necropsy, dilated ventricles were found in the brain. Bleeding brought a fall in both arterial and cerebrospinal fluid pressures, but in slow reduction of blood pressure there occurred no change in cerebrospinal fluid tension. Withdrawal of 5 to 10 cc. of spinal fluid brought usually a fall of 20 mm. in the arterial tension of normal persons and of 40 to 60 mm. in hypertensive patients. No change was found in hypotension. As Kahler (235) has pointed out, increased blood pressure after removal of cerebrospinal fluid may be the response in "anatomic hypertension" with pronounced vascular disease.

The association of venous pressure with that of the cerebrospinal fluid was found by Tzanck and Renault (476) much closer than arterial tension. They recorded an agreement within 1 or 2 mm. Hg, pressures of 26, 28 and 30 in the cerebrospinal fluid corresponding respectively to levels in venous pressure of 25, 29 and 28 mm. This agreement accords with the close anatomic relations of the venous plexuses and the cerebrospinal fluid.

Ocular tension and the pressure required to obliterate the pulsation of retinal blood flow from the central artery have been studied and have not been shown to exhibit a strict parallelism with cerebrospinal fluid pressure.

Block and Oppenheimer (71) found that there is a tendency for ocular,

cerebrospinal and blood pressures to rise and fall together. A fall in ocular tension usually followed spinal puncture, but, confirming Kahler, there was an occasional rise in ocular and arterial pressures. In a patient with uremia during convulsions the cerebrospinal fluid pressure was found to be 60 to 80 mm., it fell to 30 mm. after the convulsions ceased. In another uremic patient the cerebrospinal fluid tension was 47 mm. during, and 7 mm. after, the paroxysms.

Bailliart (42) and his co-workers, with the former's dynamometer, estimated the pressure in the central retinal artery to be 60 to 75 mm. systolic, and 30 to 35 mm. diastolic, a ratio of approximately 2:1 which they found tended to approach unity as cerebrospinal fluid tension increased. Their experience was that lumbar puncture stopped headache and nocturia concomitantly with lowering arterial pressure.

While polycythemia, with its increased volume and viscosity of blood, has been considered as a cause of increased blood pressure since the time of Geisböck, Brown and Giffin (89) found only 3 instances of mild hypertension in 14 patients who varied in age from thirty-seven to sixty-three years. Rowntree (431) cites Peacock's series of 8 cases of hypertension in 50 persons with polycythemia, and regards this incidence to be too high to be accidental. Marked reduction of red blood cells and blood volume, in one patient of fifty-seven years, brought no change in pressure.

Ashe (35) has called attention to three types of hemoglobin and red blood cell findings in hypertension, depending, he believes, on the predominance of renal, myocardial, or cerebral features. In renal insufficiency, from whatever cause, low hemoglobin and red cell values were the rule. Brown and Roth had previously pointed out injury to the hematopoietic system as one of the indications of the constitutional nature of chronic nephritis. In myocardial failure, Ashe found that the hemoglobin was low, but venous stasis was responsible for a high red cell count. In a "brain group," high normal or even polycythemic blood counts and hemoglobin were present. Ashe suggests the possible diagnostic value of the morphologic study of the blood in coma, when cerebral or uremic etiology is in doubt, as well as in the recognition and prognosis of less advanced conditions. Sedimentation studies have not been found helpful in circulatory diseases (F. Groedel) and no significant changes in surface tension of the blood were noted by Nichols (363) in patients with high pressure.

CHAPTER V

Chemical Factors in Hypertension

The search for chemical substances which, through stimulation of the vasomotor center or by direct action on the peripheral vessels, might cause hypertension, began with the study of urea, the accumulation of which in the blood of animals after nephrectomy was noted by Prevost and Dumas in 1821 and then by Bright and his Guy's Hospital colleagues in patients with advanced granular kidney. Excess of uric acid in the blood in nephritis was suggested, in 1848, by the string test of Garrod. In 1850, Johnson, seeking a cause for the thickening of the renal arterioles, became a champion of toxic retention. After Strauss, in 1902, demonstrated quantitatively the increase of the non-protein nitrogen of the blood in acute and chronic nephritis, and particularly in uremia, it seemed that the methods of chemistry might prove to be the key to the unsolved etiological problems of hypertension.

Such hopes have not been realized. Of the many pressor substances which have been proposed—adrenalin by Schur and Wiesel, urea by Widal, sodium chloride by Ambard, glucose by Neubauer, uric acid by Kylin, cholesterol by Chauffard, calcium by Falta, guanidine, most recently of all by Major—none has been accepted with assurance. Neither by exhaustive studies of these or other products of metabolism, nor by the feeding of dietaries rich or deficient in the particular substance to be investigated, has any clear and definite relation to high blood pressure been established. Notwithstanding this failure, after prodigious effort, to explain hypertension on a chemical basis, the relation of the metabolites to blood pressure has been, and remains, one of the most interesting fields for clinical investigation.

NITROGEN METABOLISM

As evidence of the state of kidney function or the progress of renal insufficiency, the study of non-protein nitrogen, urea or creatinin in the blood has an extremely useful function, but throws little or no light on the causation or nature of high pressure. Urea, for example, usually has nothing to do with the production of uremia, except in large doses experimentally (465). In patients, the uremic state appears uninfluenced by the most marked variations in the urea content of the blood. Additions of urea to

the diet do not cause renal hypertrophy. Yet estimations of blood urea, repeated at intervals, give invaluable information of the course of the patient with kidney disease (299). When combined with the determination of urea in the urine (MacLean index and Ambard constant) the most delicate variations in renal function can be determined (162, 286). Lemiette (280) regards 50 to 100 mgm. as the "azotémie d'alarme;" fixed above 100 mgm., there is a life expectancy of eighteen months; above 200 mgm. a few weeks.

Uric acid occurs in hypertension with a frequency which recalls the observations of the older English clinicians upon the association of gout and vascular disease. In 110 cases of chronic hypertension, Fishberg (153) found hyperuricemia (over 3.5 mgm.) in 39 per cent, but the symptomatology and course of these patients, and the necropsy findings were not different from the group with normal uric acid. Major (310) found the blood uric acid over 4 mgm. per 100 cc. of blood in two-thirds of a series of 170 hypertensive patients without frank nephritis. The normal excretion of exogenous uric acid in hypertensive patients with hyperuricemia but no increase of blood urea led Hitzenberger and Richter-Quittner (203a) to conclude that diminished excretion by the kidney was not the factor. Kylin (261) has concluded that the level of uric acid in the blood is dependent on endogenous purin metabolism in opposition to those who regard hyperuricemia, as it occurs, for example, in eclampsia (395, 455), as the earliest sign of impaired renal function.

Spasm-producing substances of the nature of protein have been isolated by Foster (159) from the blood of patients with uremic convulsions, and by Hülse and Strauss (217) from the blood of persons suffering from malignant nephrosclerosis ("white" hypertension). The former substance was a crystalline base which produced convulsions in animals. The latter was a polypeptide which was not found in the "red hypertension" of benign nephrosclerosis. Therefore its presence was suggested by Volhard (483) to be the cause of the severe spastic phenomena of the malignant type of disease. Foster's work appears not to have been confirmed though Danzer (109) recently reported a pressor substance in the blood of hypertensive persons. Jackson (222) and his co-workers, in 34 hypertensive patients, and 16 normal controls, have found polypeptide values much lower (0.7 to 0.8 mgm. per 100 cc.) than the normal value of Blau (3 mgm.) and in decided contrast with the pathological level of 30 mgm. reported by Hülse and Strauss. Amino-acid values have been found normal, with or without retention of urea and creatinin (441).

In 1924, Major (305, 307) observed that the intravenous injection of methyl guanidine sulphate, in the proportion of 0.1 to 0.2 gram per kilo

of body weight doubled or tripled the blood pressure of the dog, and that this elevation often persisted for four or five hours. The marked arteriolar constriction thus produced could be followed ophthalmoscopically. Section of the vagi and destruction of the medulla did not prevent this pressor action.

In the blood, the normal value of guanidine is found by Major (310) not to exceed 0.2 mgm. per 100 cc.; and averages about 0.1 mgm. In 15 patients with chronic nephritis and hypertension all showed an increase in "blood guanidine" from twice to eleven times the normal, while in 80 persons with uncomplicated hypertension, 61 per cent showed values which were above

TABLE 3

Normal values for chemical constituents of blood

SUBSTANCE	MILLIGRAMS PER 100 CC.
Nonprotein nitrogen	25.0 to 35.0
Urea nitrogen	10.0 to 15.0
Uric acid	1.0 to 3.5
Creatinin	1.0 to 2.5
Guanidine	0.1 to 0.2
Polypeptide nitrogen	0.8 to 3.0
Amino-acid nitrogen	5.5 to 8.0
Sugar	70.0 to 120.0
Carbon dioxide combining power	50.0 to 70.0*
Cholesterol	140.0 to 200.0
Plasma chlorides (as sodium chloride)	570.0 to 620.0
Blood chlorides (as sodium chloride)	450.0 to 520.0
Calcium	9.0 to 11.0
Potassium	18.0 to 24.0

* Volumes per cent.

normal, though lower than in nephritis. In 330 patients grouped as essential hypertension, without increase of non-protein nitrogen, urea or creatinin in the blood and an average phenolsulphonephthalein output of 64 per cent in two hours, there was a deficienct excretion of creatinin (creatinin is the acetic acid anhydride of methyl guanidine) in 39 per cent, after the intravenous injection of 0.25 gram of creatinin. In a smaller number of hypertensive patients methyl guanidine as a test substance was excreted subnormally (309).

At the present stage of Major's work the identity of the minute amounts of the substance found in the blood appears not altogether clearly estab-

lished. The question also remains open as to whether the deficient excretion of guanidine precedes the hypertension or is the result of hypertensive renal disease. Howard and Rabinowitch (213) in one patient found that blood pressure fell without corresponding change in blood guanidine.

BACTERIAL TOXINS

Substances which from their chemical behavior are apparently amines have been found by Koessler and his co-workers (256, 285) in the filtrates from bacterial growth—especially from strains of typhoid bacilli and streptococci,—to cause a marked rise of blood pressure, as well as intense arterial constriction in vitro. Other filtrates, acting like histamine, caused arterial constriction in vitro, but in the animal a fall of blood pressure. Still others caused selective bronchiolar spasm, and in some cases contraction in both bronchial and arterial smooth muscle. Since infected tonsils, sinuses or bronchial mucosa may be looked upon as tissue cultures in vivo, from which absorption into the body is always possible, an etiology is suggested for the infectious type of bronchial asthma and for certain forms, at least, of arterial hypertension.

Anderson (28), reviewing the work of his numerous predecessors, has carried out in rabbits the most recent study of changes in blood pressure and metabolites following removal of two-thirds of the kidney substance, an amount which largely removes the factor of safety. In the control series of rabbits, fed upon a normal diet, retention of creatinin and urea became progressively greater until death, but in spite of renal insufficiency, the blood pressure did not increase. It was notable that sclerosis of the aorta did not appear in this series of animals.

When diets containing 30 per cent protein were fed, the concentration of metabolites led to extensive aortic atherosclerosis, which did not extend to the smaller arteries. There was no elevation of blood pressure. In normal animals the high protein diet brought hypertrophy of the kidneys without retention of nitrogen.

Strouse and Kelman (466) studied the effects of high protein intake, up to 150 grams a day, in hypertensive patients. No related changes in blood pressure were evident. There was no increase of non-protein nitrogen or urea in the blood and no damage to renal function. MacLean and others have reported the same findings. The clinical observation is common that a meat-free diet continued for months accomplishes nothing except dissatisfaction and partial starvation of the patient; the hypertension remains unchanged. Only when renal insufficiency is present does the severely restricted diet become warranted.

Newburgh and Clark (361) have recently shown that the amount and kind of protein, and the duration of feeding, are three important things which determine renal injury. In white rats, a diet high in urea over a year brought no evidence of renal injury, as other workers had previously shown, while a diet containing 75 per cent of dried liver produced a granular kidney in less than one year. Casein produced only tubular injury in sixteen months. Beef had an intermediate effect. The explanation is suggested by Newburgh and Marsh (360) that cystine and tryptophane, amines in which casein is poor and muscle protein rich, are nephrotoxic.

The liver diet, in the hands of Nuzum and his co-workers (368) produced in the rabbit hypertension and later arteriosclerosis in a few months time. Animals fed on grain developed similar changes more slowly, and those fed on soy bean remained free from arteriosclerosis. The factor of cholesterol (Antischkow) was eliminated since this lipoid is not present in grain. Rather than to the direct effect of excessive protein, the occurrence of vascular disease is attributed to disturbance of the acid-base balance of the body, inferred from an acidity of the urine 100 to 1000 times that of the body fluids. On the alkaline side, also, it is stated, long continued imbalance may cause moderate hypertension and kidney damage, but not arteriosclerosis.

That total extirpation of the kidneys does not necessarily bring a rise of blood pressure was shown by the older experiments of Mosler and Backman (Kylin). Cash's (98, 99) work tends to show that the products from the traumatized renal tissue remaining after operation are the cause of the heightened tension.

HYPERGLYCEMIA AND HYPERTENSION

In 1904, in opposition to Potain, Janeway (224) stated his impression that diabetes had no influence on arterial tension. Then, as later (225) he had observed that hypertension was present frequently in mild elderly diabetics, and absent in severe diabetics usually of younger age. After almost as much discussion as has been given to kidney disease and nitrogen metabolism, there is still no unanimity of opinion regarding the true relation of blood sugar and blood pressure.

Mosenthal (346) has recently reviewed some of this literature and added his own observations. In diabetic patients who have been followed for as long as seven years and in others whose blood pressure was observed during the test for glucose tolerance, he found that an excess of blood sugar does not result in an increase of blood pressure. On the other hand, Herrick (198) describes as a clinical entity the association of hyperglycemia, hypertension, obesity and vascular disease.

That both diabetes and hypertension are likely to appear at the same period in life—predominantly in the fifth decade—suggests at once the possibility of a common etiologic basis. As Neubauer (357) proposed, and as has recently been revived, it is possible that both result from the excessive action of the suprarenals. Are both evidence of vasoneurosis, Kylin asks, or is the diffuse hypertensive vascular disease the cause of the insular degeneration in the pancreas? Von Noorden (367) finds that in the family of the hypertensive diabetic, diabetes is just as likely to occur in the members who are not hypertensive. Between hypothetical "pancreatogenous" and "neurotic" forms of diabetes, he finds no difference in response to the same methods of treatment.

Age is undoubtedly a factor that confuses the statistics dealing with the joint incidence of diabetes and hypertension. Adams (3) found in 1001 diabetes patients at the Mayo Clinic, that 16.2 per cent of the males and 26.7 per cent of the females had a systolic pressure over 150 mm. in contract with 2.4 per cent and 4.3 per cent, respectively, for "normal" controls consisting of life insurance applicants. Diastolic pressures followed relatively the same ratio. Almost an equal percentage of patients had hypotension (below 110 mm.) 15.6 per cent of the men, 19 per cent of the women, compared with 2.5 per cent and 8.1 per cent in the control group. When these pressures were averaged, there was no significant difference between the "normals" and the diabetics. Loss in weight could be eliminated as a factor, since young undernourished patients formed a small part of the series, and blood pressures were usually obtained soon after admission. Consequently high pressure in diabetes is only half the picture and occurs predominantly only after forty years. The other half is that before forty years hypotension is much more common in diabetic than in normal persons.

Von Noorden found 46 per cent of his diabetic patients with blood pressures above 140 mm., 22 per cent of these were under, and 50 per cent were over fifty years of age. Comparative statistics for non-diabetics by Hitzenberg show 20 per cent hypertensive. Pressures over 180 mm. are shown to be much more frequent in diabetics. Von Noorden states that diabetes is likely to begin a decade later than usual in persons with hypertension.

At forty years, Kylin draws a line between juvenile and senile diabetes. In the first group the incidence of hypertension was only 7 per cent. Of the older group; 88 per cent had pressures over 140 mm. and 48 per cent over 180 mm. Marañon (313) found the systolic pressure had reached 180 mm. in 16.6 per cent of his diabetic patients before forty, in 54 per cent thereafter. In patients under thirty-five years, Joslin (232) found an

average blood pressure slightly below normal; at this age it rises slightly above normal, and increases with age. Under fifty years, 14 per cent were above 150 mm., 40 per cent after fifty years. Kramer (258), in 500 diabetics, found 39 per cent with systolic pressure over 150 mm., and only 4 per cent of these were under forty years. Of 225 non-diabetic hypertensives, 14.3 per cent were under forty. Here also is the observation that hypertension delays the appearance of diabetes. It suggests again Lange's (267) distinction between a functional hyperactivity during the period when hypertension is pure, and the decrease in function, in direct proportion to the development of the secondary vascular changes. There is an intermediate stage, a prediabetic period, when diminished carbohydrate tolerance may be demonstrated in the hypertensive patient (371).

In hypertension, however, diabetes is much less frequent than the converse. In 161 patients with hypertension Major (310) excluded 7 frank diabetics, and in the remainder found 9 patients with a blood sugar over 110 mgm. and only 6 with blood sugar over 120 mgm. Paullin (393) found diabetic incidence of 4 per cent in Atlanta and Westphal (495) the same percentage in Frankfort. Kahler (234) found normal blood sugar in hypertension, except in the complications of apoplexy, uremia, eclampsia and high pressure stasis, where irritation of the centers was assigned as the cause. Peiser (396) found the blood sugar curve elevated only in uremia.

In acute glomerular nephritis Kylin (261) found normal sugar values, but in hypertension he is a champion of the Neubauer school, though his acceptance of values over 100 mgm. as early hyperglycemia are partly explanatory of his position. In 22 hypertensives, Marañon (313) reported 63 per cent with blood sugar over 130 mgm. Härle (184) found true hyperglycemia in a quarter, and the upper limits of normal blood sugar in another quarter of patients with hypertension. Hitzenberger and Richter-Quittner (203a) find the blood sugar "regularly elevated in vascular hypertension, often with a high uric acid. Mild, and sometimes marked hyperglycemia occurs in chronic nephritis and is ascribed to a heightened renal threshold (396)." Chloride and nitrogen retention may accompany.

OBESITY

The close association of obesity and diabetes has its counterpart in the correlation of overweight and hypertension. Aubertin (37), Barker (47), Bauman (54), Foster (161), Herrick (198), Master and Oppenheimer (314), and Terry (469) have contributed data which show how frequently abnormal tension is encountered in the obese. The most remarkable incidence was in Aubertin's series of 70 elderly fat women in a home for the aged: there

were only 5 who had a blood pressure below 150 mm. The average age was sixty years. Yet, important as it is to recognize that reduction in weight is one of the most effective means of helping the hypertensive patient, not all are convinced that obesity influences hypertension more than does hyperglycemia. Remove the factor of age, and in young obese persons hypotension occurs as often as it does in diabetes (214). Mosenthal (346) takes a conservative view and supports Symond's statistics of blood pressure for all ages which show a systolic average of 134.4 for the obese and 126.9 for normals.

In a series of 3397 patients which Hurlin and I analyzed, there were higher blood pressures in the various age groups as weight increased (table 2).

Neither glucose nor fat possess a pressor action; rather must diabetes, obesity and hypertension be regarded as the expression of underlying abnormalities of metabolism; more often than not inborn (176), each perhaps a unit character; not necessarily occurring together, but when they do, placing a special strain through hyperglycemia, subnormal oxidation or increased tonus respectively, upon selected parts of the organism.

EPINEPHRIN

In 1907 Wiesel and Schur ventured to predict that high blood pressure, hypertrophy of the heart and the vascular changes in the kidney would be found related to increased activity of the chromaffin system. Janeway (225) traced the development of the "beautiful dream of hyperadrenalinemia" and concluded, in 1913, that it was fruitless, by available methods, to attempt to seek epinephrin in the peripheral circulation.

At the same time that clinical interest has been repeatedly drawn to the remarkably syndrome of paroxysmal hypertension associated with suprarenal tumors (382, 140, 403, 478), with cure by surgical removal, a certain amount of reassurance for the epinephrin theory has been offered by the investigations of the physiologists and pathologists.

Goldzieher (175), long a student of the suprarenal gland, has recently re-emphasized the hypertrophy of the suprarenal veins in hypertension, and Allen (11) has added confirmatory measurements as evidence of the increased discharge of epinephrin from the glands. In certain cases of hypertension, but by no means consistently, there is present suprarenal hyperplasia and hypertrophy, in which cortex shares as much as medulla. Removal of both glands during life has been followed by no fall in blood pressure. Possibly the animal's death in a few days at most prevents the experimental insufficiency to acquire a chronicity comparable with Addison's disease. At any rate, Stewart (458), in a summary which leaves few loop-

holes for loose speculation, says that "no function indispensable to life is performed by the medulla," and that there is "no foundation for the view, almost invariably expressed in clinical writings, that Addison's disease is due to loss of epinephrin." No symptoms are produced by section of the nerves supplying the suprarenals, and even if the medulla is completely extirpated, the animals remain in good health. Stewart finds no evidence that an increased output of epinephrin is even a perceptible factor in emergencies and the accompanying stress of emotion. The possibility is suggested that the abundant nerve control of the medulla (the cortex functions perfectly when denervated) is not to keep the concentration of epinephrin in the blood up to a certain beneficial level, but to keep it below a harmful level.

It follows, therefore, that the clinician ventures at some risk upon ground which the physiologists are contesting (212), but it remains permissible to assume that under disturbed conditions, the suprarenal puts forth excessive amounts of epinephrin. In no other way, can the "suprarenal syndrome" be adequately explained, and what is true of the acute attack of hypertension offers an hypothesis at least for the chronic elevation of blood pressure.

There is no difficulty in demonstrating epinephrin in the blood of the suprarenal vein, but it soon becomes so dilute or is so rapidly used up that its detection in the circulation has always offered the greatest obstacles. In frog perfusion, for example, Hülse (217) found no change in blood flow whether he used arterial blood from normal men or from patients with acute and chronic nephritis, or essential hypertension. This method Högler (206) criticizes and points out the advantages of the use of strips of intestinal muscle, obtaining inhibition of persistalsis with an epinephrin solution of 1:200 million, while substances formed during clotting have the opposite action and cannot confuse the results.

In the unanesthetized dog, Dragstedt (118, 119) and his associates have demonstrated that a pressor effect can be secured and maintained during the injection of 0.2 to 0.4 cc. per minute of a 1:1 million epinephrin solution. This amount and rate corresponds to the average epinephrin output of the dog as determined by Stewart and Rogoff (458). The same amount in etherized dogs, Hoskins and McClure earlier had found, gave a depressor effect, and five times the amount was necessary under these conditions to raise blood pressure. Rogoff (421) has shown the association of acute cerebral anemia with an increased output of epinephrin. Localized mechanical pressure on the medulla and general rise of cerebrospinal fluid tension produced rise in blood sugar without change in blood pressure in the experiments of Tychowski and Crowell (475).

SODIUM CHLORIDE

Emphasis was placed on the retention of sodium chloride as a factor in raising blood pressure by Ambard and Beaujard in 1904. This hypothesis and the dietary restriction of salt in the treatment of hypertension, to which it led the French clinicians, has been warmly sponsored in this country since 1920 by Allen (12) and his school.

The pressor mechanism of salt is not at all clear. Allen has suggested that sodium chloride raises peripheral resistance either by producing edema in the endothelium of the small vessels or through increased arteriolar tonus. It has been pointed out, in opposition, that where the edema of salt retention is most manifest, blood pressure is low (344).

Evidence for and against the pressor rôle of sodium chloride, as in the case of other metabolites, has been based largely upon the therapeutic test. Allen and Sherrill (14), in 1922, reported the results of sodium chloride restriction in 180 cases of hypertension. Normal blood pressure was restored in 18.9 per cent, improvement resulted in 41.9 per cent, transient benefit was obtained in 8.9 per cent and complete failure occurred in 30.5 per cent. An additional 212 cases were reported on by Vogel (481) in 1928. Of these 212 cases, 156 patients (73.5 per cent) improved during the initial period of treatment, usually two or three weeks in duration, and 55 (or 26.5 per cent) showed no appreciable reduction in pressure during this time; though at home, after a longer period of careful diet, some of these showed reduction in pressure or relief of symptoms. Favorable reports have been offered by other observers.

Excluding hypertension which was associated with renal insufficiency and with diabetes, Allen made an arbitrary division of his patients according to the initial concentration of plasma chloride. Above 580 mgm. per 100 cc. of blood, the prognosis was better than when the chloride level was below 580 mgm. Vogel's failures also fall in this group with the lower chloride level and in the patients with nephritis or renal insufficiency.

The lack of relationship between blood chloride values and the height of blood pressure has been shown by O'Hare and Walker (373), by Mosenthal and Short (344), by McLester (320), Stieglitz (460), and most recently by Berger and Fineberg (62). The last workers report the results of varying the sodium chloride intake of 11 patients with hypertension, one patient with nephrosis and one patient with acute glomerulonephritis and hypertension. The range extended from less than 1 gram of salt per day to 30 grams per day. In only one patient did the salt-poor diet bring an appreciable fall in blood pressure during periods of observation extending from two to five weeks, nor did the initial relation of plasma chlorides bear a relation to the

subsequent course. Administration of salt orally and even intravenously had no effect on the blood pressure level. In the patient with nephrosis the edema, but not the blood pressure, varied with the amount of salt in the diet.

It is notable that in patients reacting favorably to the salt-free diet of Allen, that reduction in weight usually accompanies the fall in blood pressure. Where there has been a salt and water retention associated with edema, particularly of the invisible type, Vogel (481) suggests that the loss of several kilograms of weight, largely water, may be expected to improve the circulation and benefit hypertension. The conservative position has been taken, in general, that salt privation leads directly to lessened intake both of food and drink, thereby decreasing the metabolic load (161). As in the treatment of obesity, the factor which influences the high pressure is undernutrition.

CHOLESTEROL

In 1924, in an analysis of the conditions which give rise to hypertension, Westphal (495) presents the recent history of cholesterol which Chauffard, Van Leersum, Fahr and others had earlier shown to be a possible cause of high blood pressure as well as of vascular disease (Anitschkow). The work of Schmidtmann (443), who in 1922 and later fed rabbits a diet (powdered liver) rich in cholesterol, confirmed by Schönheimer (445), showed that there resulted a small but distinct rise of blood pressure, without evidence of vascular or kidney disease. This suggested to Westphal the presence of purely functional changes in the arterioles dependent on the presence of cholesterol in excessive amount. He showed in vitro that cholesterol increased and prolonged the contraction produced in smooth muscle by adrenalin. Since it was not conceivable, from the results of the great mass of previous experimental work, that either adrenalin or cholesterol alone could bring about hypertension, a synergetic action of the two was postulated, and cholesterol was conceived in the rôle of a "sensitizer." As the single non-water soluble substance in the body except fat, cholesterol in theory is enabled to envelop the cell with a hydrophobic film which influences permeability and differences in electrical potential. As a result of greater surface tension, the muscle fiber thus coated would have increased capacity for contraction while the insulating property of the lipoid would prevent imbibition and relaxation. Thus could arise the state of hypertonus.

In 80 patients with primary hypertension, Westphal found an increased level of cholesterol (over 180 mgm.) in 71.2 per cent. Pribram found hyper-

cholesterolemia in 80 per cent of patients with both benign and malignant sclerosis. In a series of unselected hypertensive patients without renal insufficiency under my observation, Thro at Cornell and Roe and his associates at George Washington have determined blood cholesterol without being able to demonstrate any correlation with the height of blood pressure. Several of the patients with the greatest and most stable hypertension had low cholesterol values. Approximately 60 per cent, however, were above the level of 200 mgm. per 100 cc. of blood taken as the upper limit of normal. Two patients with malignant hypertension, one only with moderate nitrogen retention, showed the highest cholesterol values—344 and 364 mg.

Richard and Roesch (413) have reported findings which like those of Chauffard, Laroche and Grigaut, and Labbé, indicate that hypercholesterolemia, while often present in hypertension, is independent alike of nitrogen or salt retention and height of blood pressure. Thölldte (470) and Thomas (471) reach similar conclusions.

The extremely complex relations of cholesterol in respect to cellular metabolism and systemic disease have been given full discussion by Westphal. Practically, the work led to the resumption of the therapeutic use of the cholesterol-dissolving sulphocyanate.

CALCIUM AND POTASSIUM

In another direction, increasing attention has been devoted to the part played in vascular phenomena by the cations—sodium, potassium, calcium, ammonium—in contradistinction to the anionic chloride, sulphate and other halogens. In edema, the treatment and the promotion of diuresis by the replacement of the sodium ion by calcium or ammonium has become of great practical interest (240). Closely related physico-chemical changes appear to take place in the arteriolar smooth muscle and influence blood pressure.

Kylin (261) has reviewed and extended the study of the calcium and potassium content of the blood serum in hypertension. The normal calcium value lies between 9 and 12 mgm. per 100 cc. of blood with an average of 11 mgm. for persons over forty years. The average value for hypertensive patients is placed at 10.2 mgm. (Kylin, Jansen, Zondek). The potassium level is normally 18 to 22 mgm. per 100 cc. of blood. In essential hypertension the values rise to 22.6 to 28 mgm. Calcium values in essential hypertension, therefore, tend to fall, potassium values tend to rise: the K/Ca ratio changes in favor of the potassium. The same shifting is shown in bronchial asthma, gastric ulcer and neurosis; on the contrary, in pancreatogenous diabetes and in exophthalmic goitre, Kylin shows that the calcium

increases at the expense of the potassium. Streicher found a great rise in calcium in experimental uremia produced by urea intravenously (465).

Upon the demonstration by Kraus (259) and others that calcium increases sympathetic action and potassium that of the vagus, Kylin has ventured into the perplexing field of sympathicotonia and vagotonia in their relations to hypertension. The determination of the K/Ca ratio and the reaction of the blood pressure to adrenalin are the two chief methods. When the ratio is subnormal (1.40 to 1.80) the intravenous injection of 0.01 mgm. of adrenalin is followed, Kylin found, by a primary rise of blood pressure. When the ratio exceeds normal and rises to 2.15 to 2.50 the response to adrenalin is a primary fall, followed by a greater secondary rise. Calcium increases the primary ascending phase, potassium the descending phase. By the intravenous injection of one or the other, the response to adrenalin may, for the time being at least, be reversed in the individual case. In general, the study of this response to adrenalin has led to extremely variable reports (103, 228, 263).

Petersen and his coworkers (399a) have investigated exhaustively the blood chemistry and vascular and skin reactions of normal men and patients and have analyzed the characteristics of the "sympathetic" and "parasympathetic" groups and of exophthalmic goiter.

Kylin draws the conclusions that in essential hypertension the blood pressure response to adrenalin varies significantly from the normal reaction, the "potassium-vagus" factor predominating over the "calcium-sympathetic" factor. Therefore, the essential nature of hypertension is to be explained by a shifting of values in the vegetative system, which, it is recalled, is composed, according to Kraus, of electrolytes, hormones, and sympathetic nervous system taking part in the regulation of cell equilibrium. In any of these components, a primary disturbance may be postulated, but in none has the means yet arrived to give answer to the complex problems of physical chemistry.

Upon the therapeutic side, however, certain progress has been made. Kylin has reported favorable results from the use of atropine and calcium, the former to paralyze the vagus endings, the latter to provide the conditions for sympathetic stimulation. Altnow and O'Hare (19) have failed to secure similar results, but benefit from calcium therapy, with or without atropine, has been reported by Fahrenkamp (148), Matthes, and Loewenstein (289).

Addison (6, 7) has reported excellent therapeutic results by substituting the potassium ion, in prescribing citrate, bromide, and chloride, in place of sodium which, he found, increases muscle and nerve irritability in patients with hypertension.

THE MENOPAUSE

Hypertension of the menopause has been described as a clinical type by numerous authors, but as in the analogous cases of the influence of the suprarenal, pituitary, thyroid and testicular glands, on blood pressure, there are usually confusing factors to obscure ovarian function. Study of the incidence of hypertension showed a sharp rise at about the age of forty in a series of 1000 women analyzed by the author, and approximately a decade before the same rise occurred in men (169). Munk states that the earlier the climacteric appears, the more frequently is it accompanied by high pressure. He notes, as have others (406), the frequent association of myomata of the uterus and hypertension. Alvarez and Zimmermann (22) found that women with disorders of the sexual organs had a level of blood pressure distinctly higher than normal women. Ovarian secretions tend, it appeared, to repress the hypertensive process. Whether this effect is through the individual action of the gland or by maintaining balance of the endocrine system cannot be determined. Hopkins (209) described as the "menopausal type" the healthy-looking, over-weight, energetic, nervous women of the upper social strata, "used to good living and fond of life but nevertheless subject to many worries and anxieties." Riesman drew a similar picture (416).

The gynecologists are hopelessly divided. Nielson (364), LeConte (276), and Schlesinger (440) represent the advocates of a specific form of hypertension.

But Lehfeldt (279) found on analysis of 111 patients that fluctuations in blood pressure occur in 25 per cent irrespective of artificial, or natural menopause, but that only 14 per cent showed a rise above 140 mm. There was no correlation of myomata and blood pressure. Pellissier (397) and Bell and Clawson (57) oppose the idea of climacteric hypertension. Gelman (173) finds the same incidence of high blood pressure in both sexes. Hypertension is more frequent in the heavily laboring classes, and is not related to the menopause. F. Müller (351), in discussing the association of myomata with heart disease and high blood pressure, states that no pressor substance was found by Böhm in a uterine fibroid freshly removed from a hypertensive woman.

Polak (406) found no correlation between myomata and hypertension, nor was removal of the ovaries followed by a permanent rise of blood pressure.

HYPERTENSION AND PREGNANCY

Hypertension with little or no evidence of kidney disease was found by Herrick and Corwin (199) in 60 per cent of cases of late toxemias of pregnancy. In 165 of these women, who were followed in some cases as long as six years postpartum, there were discovered signs of chronic cardiovascular disease in 74 per cent, including persistent hypertension in 37 per cent. The data show that the higher the blood pressure during pregnancy the more likely it is to become permanent and to be associated with vascular disease. Herrick takes the position that the reaction to the strain of pregnancy anticipates the response to the wear and tear of life.

Peckham's (395) investigation of the state of 74 patients one year after eclampsia revealed "chronic nephritis" in 23 per cent. In 75 per cent of these women, the blood pressure was normal within three weeks of the termination of pregnancy. Nevertheless, of this number several went on to develop persistent hypertension and signs of kidney damage. The difficulty, indeed inability, to distinguish between mild toxemia and one that will lead to eclampsia is admitted. The sequelae, however, bear definite relations to the age of the patient and the severity of the eclampsia measured by height of blood pressure and degree of albuminuria. Retention of nitrogen and duration of toxemia were not found reliable guides in prognosis. In one patient, the uric acid rose to 12 mgm. without evident significance.

When the systolic pressure remained below 170 mm., no sequelae developed. The percentage was 15.4 after pressures between 170 and 200, and rose to 48.1 when the blood pressure was over 200. With a blood pressure of 200 mm. and 10 grams of albumin in the twenty-four hour urine, 80 per cent of the patients went on to develop nephritis. The incidence of subsequent chronic nephritis was 11.8 per cent for patients under twenty years, 13.8 per cent in the third decade, and then increased remarkably. For the age period of thirty to thirty-nine years, no less than 63.6 per cent developed nephritis, and 66.6 per cent of the women over forty years had the same unfavorable course.

In an investigation of the hypertension of pregnancy, Stieglitz (459) found that hypocalcemia plays no major etiologic rôle, though there is a relation between minor variations in arterial pressure and blood calcium, as in lactation, when pressure goes up and calcium falls. Four types of hypertension are described by Stieglitz: (1) a benign form, occurring early and rising gradually without serious intoxication; (2) a late malignant form, leading to eclampsia; (3) hypertension associated with preëxisting vascular and usually renal disease; (4) hypertension associated with complications such as toxic goiter and cardiac disease.

Of the substrata of eclampsia Stander (455) gives the following summary: "Eclampsia is very seldom associated with nitrogenous retention in the blood, and where the non-protein nitrogen is elevated, it is probably the result of kidney injury caused by the eclamptic outbreak. The same holds true for blood urea nitrogen. An increased uric acid and decreased carbon dioxide combining power are the outstanding findings in the blood chemistry in eclampsia. The blood sugar is sometimes normal, but is often elevated, according to most authors, although some claim that hypoglycemia invariably accompanies the disease. The author believes that the weight of evidence is in favor of a normal or elevated blood sugar. Blood lactic acid is elevated in eclampsia. There is some controversy regarding amino-acids in the blood, but it appears that the disease is not associated with disturbed deaminization. The polypeptide nitrogen has not been satisfactorily worked out. Creatin and creatinin metabolism is not markedly upset. The blood chlorides show a disturbance where the disease is accompanied by edema. The only abnormal findings in the cations is a slight elevation in the phosphorus-calcium ratio, due mainly to an increase in phosphorus. The blood colloids reveal a disturbance consisting of a shifting in the protein fractions in favor of globulin, fibrinogen, and euglobulin at the expense of albumin. Fats and lipoids show no greater disturbance than is noted in normal pregnancy. The very meager work on the hydrogen ion concentration of the blood in eclampsia points to a true acidosis in some cases. No toxin in the blood or urine has been isolated. The only abnormal finding in the urine is a slight upset in the nitrogen partition due to a decrease in the urea nitrogen. The various blood disturbances so far noted seem to be interrelated, and deficient oxidation processes probably play a major rôle."

These statements can be translated almost bodily to the discussion of hypertension in general!

CHAPTER VI

The Incidence of Hypertension

In order to secure a broad view of the problem of hypertension in the community—its epidemiology, in contrast with its genesis and course in the individual patient—it is necessary to determine blood pressure in groups of people as nearly unselected as possible. Such a census might be expected to disclose not only the incidence of hypertension and its claims to attention as a matter of public health, but also to throw light on its nature and development through increasing knowledge of the conditions under which it prevails.

Comparative studies of blood pressure also, carried on in special groups—set apart from the general population by race, age, sex, occupation, social level, or state of health—have contributed data of value in revealing the natural history of hypertension and the influences of environment, internal as well as external.

Take, for example, the entire freedom from chronic hypertension already referred to in African negroes, compared with the prevalence of hypertensive vascular disease in the black race in America. The former live an unhurried tribal life which has maintained its even tenor for centuries. Their kinsmen were translated abruptly into a new kind of life of which the social and economic restrictions and demands serve to constitute a large scale experiment in biologic adaptation. Here, after all, infection, diet, kidney disease appear as relatively minor agents of blood pressure change in comparison with the physical and psychical effects of prolonged stress and strain. By comparison with the simpler living conditions even of a generation past, it must be evident that for all persons survival in the modern period demands criteria of fitness which place new, if not superphysiological, burdens upon many human organisms.

For the purpose of securing data in regard to the incidence of hypertension in a general city population, 2000 consecutive patients, equally divided by sex, were studied (169). They came to a general medical clinic for complaints unrelated by them to hypertension. There were the unavoidable few who had been told of, and were concerned with, their high blood pressure. Aortic insufficiency was excluded from the series and also true nephritis with hypertension. The latter is accomplished without difficulty, since the ratio of nephritic to essential hypertension of 1:11 found by Harpuder (188)

in hospital practice becomes still higher in ambulant patients. For abnormal systolic pressure the criterion chosen was 140 mm. before forty years, and 150 mm. after this age; for diastolic hypertension 90 mm. at all ages was taken as the dividing line.

The analysis revealed systolic hypertension in 15.2 per cent of the men and in 16.9 per cent of the women. Diastolic hypertension occurred in 12.6 and 16.1 per cent for the sexes, respectively.

The early appearance of primary hypertension in adolescence and its speedily increasing incidence and height in successive decades suggested a predisposition which is constantly enhanced by the changing conditions of life and environment. A rather sharp rise in the percentage of hypertensive women at forty years, and in men a decade later was an observation which Saller (435) and Riseman and Weiss (418) have confirmed. Among the men, the percentage of hypertension of 5.6 before twenty years, and of 9.6 between twenty and thirty years, became 48.7 per cent between sixty and seventy years. In the women, the percentage of hypertension rose from 1.8 and 3.0 in the second and third decades to 42 per cent between sixty and seventy. One must agree with Gelman (173) that little difference exists between the sexes in respect to the frequency of high pressure, though in Boston the incidence in women (6.6 per cent) is reported over twice as high as in men (418).

Edens (128) has tabulated corroborative data of hypertension in Munich. As unduly high pressure for young adults he accepted values of 100 plus the age in years, while following Volhard in regarding blood pressure over 140 mm. as pathologic at any age. In 2814 patients over twenty years the incidence was 14.5 per cent, not quite so high as our New York figures, and higher than Janeway's percentage of 11.2 fifteen years before, using at that time 160 mm. as the dividing line. As incidence in office patients of 9 per cent with systolic pressure of 150 mm. or more was reported by Hamman (187).

Selection, which inevitably plays a part in the practice of every physician or hospital, becomes well marked when at one extreme patients present themselves because of circulatory disease and at the other in good health or at least unconscious of physical impariment. Thus the data of hypertension in the cardiac clinic may be contrasted with that of life insurance medicine.

A study of the comparative incidence of the chief types of disease in various American heart clinics (170a) reveals that hypertension, which is often inextricably combined with arteriosclerotic disease, makes up from 30 to over 50 per cent of all the patients. In the northern cities, even rheumatic

TABLE 4

Hypertension in 2000 ambulant medical patients

(A) Incidence by age and sex

AGE	MEN					WOMEN				
	Total number	Hypertension				Total number	Hypertension			
		Systolic		Diastolic			Systolic		Diastolic	
		Number	Per cent	Number	Per cent		Number	Per cent	Number	Per cent
Under 20	39	2	5.1	1	2.5	56	1	1.8	1	1.8
20–29	239	23	9.6	11	4.6	261	8	3.9	9	3.4
30–39	310	32	10.3	31	10.0	257	30	11.6	23	8.9
40–49	190	21	11.0	25	13.1	207	46	22.2	56	27.0
50–59	133	32	23.9	30	22.5	155	57	36.7	49	31.5
60–69	80	39	48.7	27	33.7	59	25	42.3	21	35.5
Over 70	9	3	33.3	1	11.1	5	2	40.0	2	40.0
Total	1000	152	15.2	126	12.6	1000	169	16.9	161	16.1

(B) Percentage distribution of blood pressure by its height

SYSTOLIC PRESSURE			DIASTOLIC PRESSURE		
Mm. Hg	Men	Women	Mm. Hg.	Men	Women
Under 100	4.2	7.3	Under 60	5.5	4.8
100–109	13.6	14.6	60–69	19.3	22.0
110–119	26.9	24.5	70–79	41.8	35.1
120–129	20.8	17.0	80–89	20.8	22.0
130–139	15.6	13.0	Under 90	87.4	83.9
Under 140	81.1	76.4			
140 and above	18.9	23.6	90 and above	12.6	16.1
150 and above	11.8	14.5	100 and above	5.7	7.5
160 and above	7.3	10.6	110 and above	3.2	4.6
			120 and above	2.1	1.3
180 and above	4.1	5.7	130 and above	1.1	0.6
			140 and above	0.4	0.3
200 and above	2.4	3.1	150 and above	0.1	0.1
220 and above	1.3	1.2			

Table 4 shows the frequency of elevated blood pressure in unselected patients, taken consecutively by sex, as admitted to the department of medicine, Cornell Clinic, New York City. The criteria of hypertension are, for systolic pressure, 140 mm. or more below forty years, 150 mm. and above after forty years; for diastolic pressure, 90 mm. and above at all ages.

infection of the heart is only a few per cent higher than hypertensive disease, and syphilis as a rule is relegated to third place by a considerable margin.

George Fahr found in Minneapolis that 50 per cent of all patients with organic heart disease who were over forty-five years of age had a systolic pressure of 180 mm. or over, and a diastolic pressure of 100 mm. or above. At necropsy, of all heart disease not due to valvular lesions or syphilis, 70 per cent were hypertensive. Fahr offers a conservative calculation, based on the mortality statistics for the United States registration area in 1924, that 143,000 deaths in persons of fifty years and over were associated with hypertension. He comments on the fact that hypertensive heart disease is frequently incorrectly diagnosed as myocarditis or mitral insufficiency, that true nephritis, in contrast with hypertensive renal disease is rare, and that in apoplexy hypertension is present in the majority of cases.

While insurance medicine has given invaluable statistics of normal pressure, the incidence of applicants who are rejected for high blood pressure—1.74 per cent and 1.6 per cent in two companies, and in a third 2.4 per cent for men and 4.3 per cent for women—is not generally accepted as representative of the incidence of hypertension in the population at large (167). In 16,358 insurance policy holders periodic health examinations showed an incidence of 6.2 per cent with blood pressure 20 mm. above standard (122a).

Studies of blood pressure in university students by Lee (278) at Harvard, Alvarez and his co-workers (20, 21) at the University of California, and Diehl and Sutherland (112) at the University of Minnesota, have shown that the percentage of persons with abnormally high readings may run from 6.2 to as high as 20.8 per cent. Repeated observations reduce the percentage of hypertension by more than half, but the fact remains that in youth not a few candidates for high pressure later in life are found in a pre-hypertensive or early hypertensive state.

In adults, Alvarez (23) has determined the incidence of hypertension in patients with constipation without finding any relation in men, and in women even a slightly lowered mean blood pressure. Pressures were found higher in women who were sexually abnormal—with secondary sexual characters, myomata of the uterus, or pelvic diseases which had required removal of uterus or ovaries—and also in the stout, whose pressure was 12 mm. higher than in the well proportioned women and 22 mm. higher than in thin women (22). Endocrine and metabolic factors were suggested in these groups.

In 381 lead workers Mayers (317) has studied the occurrence of arteriosclerosis and hypertension. Arteriosclerotic changes in the accessible

vessels were found in 22.5 per cent, all occurring in the 227 men over thirty years. Ninety-eight men showed hypertension; under thirty years of age in 28.5 per cent, in the group over thirty years, in 23.7 per cent. There was evidence of lead absorption in 65 per cent of the hypertensives, but also in 59 per cent of those without hypertension. Hence Mayers expresses doubt of a hypertension based solely on the arterial changes due to lead.

Gelman (173), investigating the influence of occupation on blood pressure concludes that elevation is more frequent in laborers than in brain workers. He believes that the variations in pressure occurring during heavy manual labor lead to permanent structural changes. In foundrymen, exposed to excessive heat as well as hard work, in the decade between thirty to thirty-nine years 13 per cent were hypertensive (over 140 mm.), while at the same ages compositors showed 7 per cent and male teachers no hypertension. In the decade between forty to forty-nine years, the hypertensive foundry workers were 21 per cent, the compositors 14 per cent, male teachers 15 per cent. Among women teachers in the fourth decade, 5 per cent were hypertensive, in the fifth decade, 10 per cent. Weavers showed a percentage of 17 and 19 for these decades. Of 45 telephone operators between thirty to thirty-nine years 25 had pressures from 131 to 140 mm. and 4 over 140 mm. Gelman noted a hypertensive incidence of 5 to 8 per cent, largely transitory, in youth, and a steady rise for both sexes, uninfluenced by the menopause, and reaching 31 per cent between fifty to fifty-nine years.

In 464 unselected patients with pulmonary tuberculosis, Stivelman (461) found hypertension in 10 per cent. There was less hemoptysis among the hypertensives than in those with lower blood pressure. Hypertension indeed, tended to give a favorable prognosis; only 13 per cent in the group had progressive disease compared with 30 per cent in the whole number of patients.

HYPERTENSION IN CHILDREN

Hypertension in the young has a particular interest, perhaps because, in Stockard's words (462) "the rare occurrence of a typically adult disease among children may furnish a simpler clue to the constitutional diathesis than the study of great numbers of adults with this disease."

In a child of three and one-half years, with a doubtful history of scarlet fever, Schwartz (446) reported the development of a blood pressure of 250/195. There were pipestem arteries, thin tortuous retinal arterioles, old and fresh retinal hemorrhages, degeneration and edema, and cardiac hypertrophy. A course of six months ensued before death. There was no anemia, no retention of nitrogen and a phenolsulphonephthalein excretion of 56 per

cent. The blood and spinal fluid Wassermann tests were negative. The clinical picture was regarded as that of primary contracted kidney.

Nobécourt and Lébec have reported that the Ambard constant and the plasma chlorides were normal in a child of thirteen years with permanent hypertension and retinitis. They suggested syphilis as a cause.

Pellisier (398) found no stigmata of hereditary syphilis in infantile hypertension three examples of which he found in 100 children, in contrast with 21 cases of hypotension. In 16 young patients Moog and Voit (331) found constitutional anomalies in 10, such as increased reaction to adrenalin and increased basal metabolic rate. They conclude that primary susceptibility is present in such patients rather than premature vascular senility. Alvarez (24) has expressed the feeling that hereditary predisposition is at the bottom of the youthful symptoms and development of hypertension. Magniel (302) felt that scarlet fever and syphilis can often be excluded as causes of hypertension in the young and thinks that the chromaffin tissue is already overactive.

Branch and Linder (83) have reported hypertension in young patients and discussed the relationships of nephritis and vascular disease.

Amberg, (25) studying persistent elevation of blood pressure in the young, has found 6 different types:

1. Hypertension limited to the upper part of the body associated with the coarctation of the aorta. The retinal arterioles were contracted, renal function was normal. Similar examples have been reported by King, Moschowitz, Abbott, Blackford, and others.

2. Hypertension with organic cerebral lesion, for example, temporal lobe abscess in a boy of seven with a blood pressure of 175/125. After operation the blood pressure fell to 100/60, but the retinal arterioles were small several months later.

3. Essential hypertension without evidence of renal injury.

4. Malignant hypertension with rapid downward course and extensive arteriolar disease.

5. Hypertension associated with a variety of lesions of the kidney.

6. Hypertension following congestive heart failure.

HYPERTENSION IN THE AGED

As age increases, Barath (46) has shown the progressive failure in regulation of blood pressure, standardized physical and mental tests calling forth exaggerated and persisting responses. This altered physiological reaction is reflected in the incidence of hypertension in old age. Richter's (414a) more recent statistics confirm the older observations of Wildt and of Bowes

and tend to show a constant rise in systolic pressure even in the last decades of life. Diastolic pressure however, tended, in his patients to be lower than in middle life. For the age group sixty to sixty-four years, the average pressure was 138 systolic, 74 diastolic; for the half-decade eighty-five to eighty-nine years, the pressure became 161 systolic, 67 diastolic. Weitz (494) found that the incidence of patients with systolic pressure over 150 mm. rose from 2.8 per cent in the group from forty-six to fifty years to 28.4 per cent in the group from sixty-one to sixty-five years of age. In 80 men from sixty to sixty-nine years of age, I found 39, or 48.7 per cent, with a systolic pressure 150 mm. or above, 33.7 per cent with a diastolic pressure of 90 mm. or more. Of 59 women in the same decade, 42.3 per cent had systolic hypertension, 35.5 per cent showed a diastolic pressure above this level (169). Unless myocardial weakness intervenes, the tendency for hypertension to persist is evident.

CHAPTER VII

The Symptomatology of Hypertension

The recognition of hypertension by use of the manometer is easily accomplished without the expenditure of much time or any mental energy. It is only, however, by the study of symptoms, as the subjective evidence, and of signs, the objective evidence, of disease, that the physician can place himself in a position to understand his patient's own peculiar tendencies and susceptibilities, and thus offer a rational prognosis and plan of treatment.

Strictly speaking, one can say, with Christian (100), that there are no symptoms and signs of hypertension; what we observe on one hand are the general manifestations—of hereditary and constitutional nature—which precede high pressure, and on the other hand, the results of complications of the hypertensive process in the various domains of the body in the form of vascular disease and disturbed blood supply and nutrition.

Frequently moderate hypertension and, occasionally, even an extremely high blood pressure may persist over a considerable period of time without symptoms. Such was the case with an Italian laborer of fifty years who during at least a year's observation, carried without complaint, a pressure regularly over 300. This is the "hypertension solitaire" of the French (397). Bishop (67) called attention to this type of patient and suggested that the absence of symptoms and cardiac enlargement was due to congenital causes. Relatively few patients, however, perhaps those who, as Libman has shown, are relatively insensitive to painful stimuli, bear the burden of hypertension long without some evidence of its effect on mind or body. Within four weeks of the onset of severe nephritis, Traube, it is recalled, detected cardiac enlargement.

For most of us it is well to remember Allbutt's maxim that "we must know that we may see;" and MacKenzie wrote that those "who specialize in the diseases of certain organs have no difficulty in detecting symptoms belonging in their specialty in a sick person."

Consequently, it is usually true, even in the prehypertensive period, and in the early stages of hypertension when wide fluctuations of pressure are so particularly characteristic and so productive of symptoms, that information of the greatest value concerning the patient's type and reaction to environment is disclosed by a searching history and examination. In a recent dis-

cussion of the diagnosis of obscure chronic disorders, the relative importance of the history was evaluated at 65 per cent, the physical examination at 20 per cent and the laboratory data at 15 per cent.

Hypertension varies greatly in its symptomatology according to its mode of origin, its tempo or rapidity of development, its degree, and the body areas which are predominantly involved first in the functional, and later in the structural vascular changes. Literally, the circulatory disturbances incident, or subsequent, to hypertension produce a range of clinical phenomena from which no system of the body is immune and no specialty of medicine divorced.

Acute hypertension is a pure disorder of function. Usually it arises from the baseline of normal blood pressure—in suprarenal tumor, in eclampsia, in acute lead poisoning, in the crises of thoracic and abdominal pain; or as in chronic glomerulonephritis, it may appear as the exacerbation of existing high pressure. By the full development of the symptoms and signs of vasoconstriction and ischemia in a few seconds, minutes or hours, the picture of acute hypertension stands in essential contrast with that of the year- or decade-long course of the "benign" chronic disease.

Vaquez (478), among numerous other observers in recent years, has described as follows the dramatic sequence of events in paroxysmal hypertension. The patient was a man of thirty-seven years, who for three years often suffered daily attacks of agonizing cramps in legs, abdomen, heart and head, relieved only transiently by Roentgen radiation, after operation had been refused. "We had just finished auscultating the heart, of which the rhythm, rate and sounds were normal, and had taken the arterial pressure, the maximum 140, the minimum 80, when the patient suddenly cried, "An attack is coming." Abruptly the entire skin became pale, and the face, also pallid, took on the aspect of a mask of pain. The pulse increased so rapidly that we had the idea of again auscultating the heart, the signs had been completely changed in a few seconds. The rate had increased from 70 to 110 beats per minute and in place of the normal second sound at the base, there was a true aortic clangor. The sphygmomanometer had remained attached to the arm, the pressure now taken, had passed from 140/80 to 300/180. The hypertensive crises attained its acme about the third minute, then began to decline, and the manometer registered successfully 210/140, 180/110 and about the seventh minute 140/90."

At necropsy a paraganglioma was found in the right suprarenal region weighing 186 grams, while the left suprarenal gland was normal in size and structure.

In eclampsia, a form of hypertension which lacks this paroxysmal charac-

ter, but is considerably more prolonged and often persistent, is present as an integral part of the syndrome. Indeed, the underlying vascular spasm is regarded as the cause of many of the eclamptic phenomena. Usually the physician or obstetrician is forewarned by the appearance of increasing blood pressure, albuminuria, edema and abnormally rapid gain in weight. But not rarely, even under adequate antepartum supervision, it happens that the toxemia becomes fully developed in the few hours or days that have elapsed since routine examination (395). The symptoms are largely cerebral, though obviously the kidneys are effected, but vasoconstrictive effects in other localized areas, as in the domains of coronary or mesenteric arteries, are rarely seen. The onset may be entirely unlooked for, as in the case of a physician's daughter, aged twenty-one years, a primipara nearing term, who had been previously well and carefully watched during her pregnancy. A convulsion occurred as from a clear sky. Her obstetrician considered vaginal hysterotomy without delay the treatment of choice; a living child was delivered, but though the blood pressure fell to normal, a complicating pneumonia was fatal for the mother within the week. The medical man, persuaded by even one such tragic experience to advise expectant treatment and conservative methods of delivery unless intervention is urgent, finds himself supported by the results of the best obstetrical practice (455).

The classical symptoms and course of eclampsia and eclamptic hypertension are revealed in the medical notes of the following patient:

A white primipara of twenty years, seven months pregnant, was discovered with pallor, edema of the ankles, a heavy trace of albumin in the urine, and a systolic pressure of 140 mm. Against advice, she returned home instead of entering the hospital. Twenty-four hours later, she was brought in by her husband, listless, drowsy and disoriented. The systolic pressure was 170, the urine boiled solid. There was no elevation of temperature, pulse 80, respirations 18. The patient vomited the medicines given by mouth. There were involuntary passages of stool and urine. Twitching of the hands and face were observed, and the breathing became stertorous. Papillary and retinal edema appeared. During the interval in which the obstetrician was dilating the cervix by means of Voorhees' bags, colonic irrigations, catharsis, a milk diet and chloral brought no improvement. After two days, manual dilatation of the cervix was resorted to and a living child extracted. When the patient was discharged three weeks later, edema had left, there was a trace of albumin, with occasional granular casts in the urine, and the blood pressure was 115/70. There was a secondary anemia, with hemoglobin 65 per cent and red blood cells 3.9 millions.

All these various manifestations of eclampsia—epileptiform convulsions,

delirium, coma, headache, amaurosis, aphasia, pareses—are identical, as Oppenheimer and Fishberg (383) have pointed out, with the cerebral symptoms of acute lead poisoning, acute glomerulonephritis and the exacerbations of chronic nephritis with hypertension. These authors suggest for the whole group the name of hypertensive encephalopathy. Munk too advises that the term uremia be discarded in respect to these cerebral processes, which are evidently related neither to kidney disease nor to nitrogen retention (asthenic uremia of Reiss), but are caused by the high degree of vascular spasm and the resulting cortical ischemia or anemia. This functional state of arteriolar constriction the ophthalmoscope has revealed in the retina, and cerebral edema and increased intracranial pressure as causes of eclampsia, as probably of uremia, are believed to be of secondary occurrence and importance.

Acute hypertension and hypertensive encephalopathy occur also under other conditions.

In attacks of angina pectoris a rise in blood pressure is the rule and may reach a height sufficient to produce cerebral symptoms (125). In 5 young patients with rheumatic valvular disease (aortic insufficiency in all, combined with mitral stenosis in 4) Schwartz (447) reported severe paroxysmal cardiac pain and sharp increases in blood pressure, even exceeding 300 mm. Hg. Violent headache, overactive heart action, marked arterial puslation, venous distention, pallor, in one case extreme cyanosis, were outstanding features. After a "crucial period" of nine to twelve months, three of the patients became free from all symptoms of pain, and a fourth had rare attacks. The fifth died in one month of heart failure, without necropsy. In hepatic and renal colic, in the gastric paroxysms of tabes, in women who many years before had suffered from eclampsia followed by persistent high pressure (193), severe hypertensive crises have been described. The high pressure sometimes seen in cardiac failure of the congestive type (Sahli's *Hochdruckstauung*) also falls within this clinical grouping of acute hypertension (25, 324). In a recent patient with a failing hypertensive heart, the usual pressure of 220/140 was found to rise to a systolic level of over 300 mm. during the apneic phase of Cheyne-Stokes respiration.

BENIGN HYPERTENSION

Far different from this frank development of an acute, clearly exogenous form of high blood pressure is the insidious evolution of the hypertension engrafted upon a vasoneurosis of hereditary origin (45, 274).

This instability of the vegetative system, looked upon as a Mendelian character, may be dominant and throughout life determine constitutional

reactions. Placed in a recessive rôle, the transmitted character may never be brought into activity by the circumstances of environment. Beyond dispute, however, the hereditary potencies lie dormant in most of us awaiting activation sooner or later, and often with even the earliest physical or psychic strains to which we are exposed. From all those who are called "neurasthenic," or "psychopathic" or "sympathicotonic" it may well be the hope of preventive medicine, perhaps by methods of anthropometry combined with those of more refined clinical diagnosis, to determine the prospective victims of hypertension as the first step toward an adequate program of prophylaxis and protection against this and other expressions of vasoneurosis.

The prehypertensive symptoms and signs enumerated long ago by Mahomed (303) and recently re-emphasized by Kauffman (238), Alvarez (24), and Ohler (380) are well illustrated by the following patient:

A. B., a woman lawyer of thirty-two years, sought advice because she "felt cranky and irritable." Her father died of pneumonia, her mother of tuberculosis, and she was an only child. At five years she had "rheumatism"; at eight, diphtheria; at ten, tonsillitis, with a heart that "flopped;" and at seventeen, a "leak" was discovered; and several ill-defined attacks of rapid heart action occurred. She taught school and was "nervous." Upon changing her environment and studying law, she "felt fine," but at thirty, she was "knocked out" by the bar examinations. A nervous "breakdown" followed, she was "worn out and on edge," a rash, lasting for a few minutes, often broke out on her face and neck, and she was told that she had a "nervous heart" and "high blood pressure." The basal metabolic rate was found normal. She now sleeps poorly. There is a tendency to constipation. She has gained weight. Her menses are regular, with profuse flow.

The physical examination showed a girl of fair complexion, height 70 inches, weight 170 pounds, blood pressure 170/90, pulse 90, regular in rhythm. An enlarged heart was not demonstrated and no murmurs were heard. The pupils reacted promptly, the retinal arterioles were very slightly thinned and irregular. The knee jerks were hyperactive. During the examination she burst into tears and was also compelled to urinate. She asked her family physician in a little town in Iowa to write me. This letter from a "country doctor," I have since prized for its insight and philosophy: "Miss D. comes from a family that has the fear complex in several members. She herself has had occasional spells with symptoms referable to the heart since her young girlhood. Neither I nor her former old time physician could detect any special reason for the attacks. A year ago she came home

much disturbed about her heart, which was quite rapid. She was quite restless and nervous and almost afraid to move from fear of her heart. There was some rise of blood pressure not marked. She had been doing heavy mental work, had been taking examinations about which she was anxious, had experienced some disappointments in love affairs, and was reduced in weight. She was much depressed.

"We were unable to detect an organic lesion of the heart or of any other organ, and believed her trouble largely, if not wholly functional. I had taken care of her aunt, with whom she had lived since a little girl, for a similar condition and had succeeded in changing her into almost a stoic; so under the quiet of a country town, her aunt's influence, and a lot of encouragement on our part, she soon gained 25 pounds in weight and made rather rapid improvement in all her symptoms. . . . . I have tried to assure her that she had no cause to fear from her heart—even more than I was real sure of myself." . . . .

Starting thus obscurely with symptoms which are non-specific for hypertension—irritability, psychic instability, easy physical and mental fatiguability, imperfect digestion, palpitation, flushes, cold blue hands, frequent urination, possibly sexual impotence—the progressive course of hypertensive vascular disease leads slowly to three chief syndromes. These may be well defined, often advance together, or are superimposed. These types are the cerebral, the cardiac and the renal. By some considered as essential parts of the chronic hypertensive process, by others as complications, they are important because they are the chief basis of symptoms and the major causes of mortality.

Dizziness, fullness or tightness in the head, "douleur en casque," the occipital headache occurring in the early morning hours and wearing off after rising, described by Janeway, migraine or hemicrania, the sensations of throbbing and noises, are the symptoms which suggest cerebral vascular lesions.

Shortness of breath, the sensations of premature beats, heaviness in the chest, substernal pain, point to myocardial degeneration and coronary sclerosis. Frequency of urination, especially nocturia, and an excessive amount of urine, with low and fixed specific gravity (hyposthenuria), indicate involvement of the kidneys.

The occurrence of fullness, distress or pain in the abdomen (92), of cramps in the legs (intermittent claudication), of impairment of vision, are evidences of vascular disease in these several domains of the body. The symptoms and signs of diabetes mellitus arise from pancreatic arteriolar disease.

The joint and muscle pains which are called "high pressure rheumatism"

have been ascribed to regional angiospasm. Kaufmann has found these symptoms present in 33 of 48 patients, and Kylin has noted their frequency. Archer's studies (30) of the contrasting types of chronic infectious arthritis and the degenerative arthritis of the menopause, have shown how close in the latter group is the association with decreased sugar tolerance, hypertension and obesity. Which of these is cause and which effect is not clear. Of 20 patients 14 showed decreased glucose tolerance; of 9 obese patients, 7 had hyperglycemia and 4 hypertension; of 6 hypertensives, 4 were obese. In the infectious type of chronic arthritis, 15 per cent instead of 70 per cent showed decreased sugar tolerance and none were hypertensive. The menopause group, however, averaged seventeen years greater age.

How the anamnesis, by developing the background and development of symptoms, helps materially in bringing out the course of the disease and providing data for diagnosis and prognosis, can perhaps be shown by a history which has just been taken.

"M. R. C., a woman aged fifty-six years, comes complaining of nervousness. Her parents died of 'paralysis,' each at the age of eighty-five. Three brothers, aged fifty-two, fifty-three, and sixty, have died suddenly of apoplexy. Two brothers and a sister are living, with normal blood pressures.

Before she was twenty-six, the patient had borne five children. At thirty her ovaries were removed and stormy artificial menopause followed. Gall bladder attacks at thirty-five have not recurred. She gained weight rapidly. At fifty, she was rejected for life insurance because of high blood pressure. Restricted diet was advised, but not followed. In July, 1928, the blood pressure was excessively high, nausea and vomiting occurred, the patient was semiconscious for six weeks, and thereafter noticed weakness in the right side, with difficulties of memory and speech. At present she is often dizzy, is unable to climb stairs without dyspnea, has felt her heart skipping. She sleeps well and arises once to urinate. No swelling of the ankles has been noted. She is nervous, is easily upset, and afraid to be alone. She has no headaches and no disturbance of vision. The urine has been found normal on many examinations."

Hypertension is clearly a dominant trait in this patient's family, and her vasomotor instability was uncovered when ovarian function ceased. It is altogether likely that with her, as with so many, the hypertension existed for many years before it was accidentally revealed by a routine examination. A cerebral accident has supervened and her symptoms now indicate an overburdened heart muscle.

"Physical examination showed an obese plethoric woman. The ophthal-

moscope revealed thin, tortuous retinal arterioles. Heart and aorta were widened on percussion. Fluoroscopy showed the high diaphragm with respiratory excursions shallow, and an enlarged heart in a transverse position. There were muffled heart sounds, and a rate of 90, with sinus rhythm interrupted at every fourth or fifth beat by a premature ventricular contraction. The blood pressure was 200/100. The T-waves of the electrocardiogram were inverted."

While the hypertensive is a "cardiopath in the making" (131), his progress toward this end is interrupted in rather more than half the cases by vascular disease elsewhere than in the heart. The brain is the second important danger area. The kidney and the pancreas follow.

The cerebral type of hypertension has been distinguished by the "hypertensive headache," throbbing in the head, dizziness, sleeplessness, irritability, mental weakness, and sometimes psychoses and dementia. Of the objective signs, vascular spasm produces a clinical picture or group of phenomena which is of the essential nature of disturbed arteriolar function and at the same time simulates and, therefore, brings in review the structural lesions of vessels and brain substance: thrombosis, hemorrhage, cerebral edema and encephalomalacia (497).

Florence J., an example of vascular crises, or "pseudo-uremia," came under my observation at the age of thirty-eight, with a blood pressure of 250/140. She was the mother of three children and was helping to support them by making shrouds in a casket factory. Her high pressure was first discovered at thirty years, but she defied natural laws and the prognosis of the doctors by going through two pregnancies and outliving several of her physicians. During five years, she had at home and in the hospital a series of "vascular crises" during which she sank into coma and the blood pressure rose from 20 to 50 mm. Lumbar punctures were used with effectiveness, on one occasion when she was able to swallow large amounts of water and sodium bicarbonate were given by mouth as well as by rectum. Not until this woman was forty-three, did cerebral hemorrhage, with hemiplegia occur. She was a small woman, of placid temperament and courageous disposition, and seemed to have inherited good heart muscle and remarkable arterial "tubing." She was not anemic, kidney function was good, and only rarely were a few retinal hemorrhages observed. She recovered from the first "stroke" and was able to go about the city.

In discussing this "cerebral type," Munk remarks that many patients maintain that they can undergo strenuous physical exertion, even to the point of mountain climbing, without symptoms, while every slight psychic disturbance promptly causes palpitation and dyspnea. He believes that the

explanation for these differences in reaction lies partly in the person's make-up and partly in his occupation and manner of life.

The appearance of paroxysmal dyspnea, or cardiac asthma, is due to anoxemia of the respiratory center, and is now regarded as evidence of left ventricular insufficiency (S. Wassermann) rather than of venous stasis. It is a phenomenon of serious prognostic import. Relatively, it does not occur as often in hypertension as in central vascular syphilis but in absolute numbers the hypertensive form is by far the more important. In a series of 250 patients, Palmer and White (388) found hypertension present in 187. Paroxysmal dyspnea occurred in 10.7 per cent of the whole number of hypertensive patients. In the 170 patients who died, the average duration of life after this symptom appeared was 1.4 years.

ANTAGONISM OF HYPERTENSION AND ARTERIOSCLEROSIS

Lange (267), from Romberg's clinic, has carried out a series of important investigations in regard to the state and function of the heart and vessels in hypertension contrasted with arteriosclerosis. The evidence shows the hyperexcitability of the circulatory system, particularly of the peripheral stream bed, in hypertension, and the sluggish, torpid, even subnormal vascular reactions in arteriosclerosis. The work recalls Pal's remark of the antagonism between high pressure and arteriosclerosis.

The studies of Lange had to begin with the selection of cases of pure hypertension on one side and pure arteriosclerosis on the other. For the former group, the best material was found in the families of hypertensive patients. Ten relatives, for example, of a woman of thirty-two years in the hospital with apoplexy, were discovered to have blood pressure over 200 mm. For the arteriosclerotic group, persons were selected whose blood pressure did not exceed 130 mm. systolic and usually ranged about 60 mm. diastolic. The accessible arteries were tortuous and thickened, even to the point of calcification, and dilatation and increased depth of shadow of the aorta was a further criterion of arterial change.

The methods included the determination (1) of the time interval between compression of the brachial artery and cessation of capillary blood flow in the nail beds; and the effect of heat and cold upon this reaction; (2) the time between release of arterial compression and capillary flow; (3) the blood pressure response to simultaneous arterial compression in all four limbs; (4) the reaction of the vessels of the stomach wall to the introduction of 15 cc. of 20 per cent brandy, measured in terms of temperature elevation by the thermocouple; (5) the vascular reaction of the kidney determined by the tests of dilution and concentration (268).

The depression of function in arteriosclerosis, Lange concluded, gives the

clue to its manifold clinical phenomena, which he traces back, not to the organically narrowed vessels, but to a primary weakness of the media. Conversely, the vascular hyperirritability in the patient with hypertension is apparently based upon excessive sympathetic stimulation of the musculature of the small vessels. The results have practical importance because they reveal latent tendencies and preclinical disturbances. In a girl of seventeen years, for example, who had been sent to the hospital, in order to have a pregnancy interrupted because of heart disease, no lesion was found and the blood pressure was 110/80. Nevertheless, the tests showed characteristic vasomotor hyperactivity, and three years later, at follow-up, the blood pressure had risen to 160/90. Furthermore, the methods may serve to show the quantitative vascular changes in the course of hypertension by measuring the alterations in function.

In addition to the symptoms of vasoneurosis, and to the distinguishing vascular reactions of the potentially or actually hypertensive patient, there are certain objective signs to be obtained by the methods of clinical anthropometry.

From his studies of constitution, Draper (120) states, among many interesting things regarding body types, that hypertension-nephritis people are differentiated from other structural builds by their relatively narrow faces and broad eye zones. People who are predisposed to tuberculosis have the same narrow head but eyes set closely together. By contrast, gall bladder people have a wide rounded countenance with narrow set eyes; pernicious anemia occurs in conjunction with a wide face, wide jaw angles and widely set eyes, and gastric ulcer is intermediate. The informed clinician, Draper writes, can observe these differences between the faces of his patients by analyzing separately the effect of soft parts and expression, and of relative differences in the facial indices and the placing of the eyes.

Carrying on such a study in eclamptic women, Draper (121) and his coworkers found that hypertension people are larger, heavier, and more masculine—more of a "pituitary type" than are people with nephritis. Changes in the bony skeleton in the direction of acromegaly or gigantism were suggested. Hyperactivity of the pituitary when the ovaries become inactive during pregnancy or when they cease to function at the menopause is a possible hint at the etiology of hypertension.

In the main, "the aggregate of hereditary characters influenced more or less by environment," which Draper calls constitution (Jonathan Hutchinson's older "diathesis" or "persisting morbid proclivity"), appear to bring functional or primary hypertension and nephritis into intimate clinical association. Perhaps, after all, nephritis, though it seems to rise from a purely exogenous cause (infection), does take root in soil which, as with hypertension, has been prepared for it.

CHAPTER VIII

The Clinical Study of Hypertension

If only a few meager signs and symptoms mark the person whose constitutional tendencies will, the environment so disposing, lead to hypertension, the sequelae and complications of high pressure give rise to a wealth of clinical phenomena. No system or organ of the body escapes in some measure the consequences of persistent hypertension.

Vessels and heart bear the brunt of the burden. The history, past, present, and future, of the hypertensive patient is written in the changes in his arterioles. The heart, for its part, endures a double insult. At the same time that its coronary arteries share in the progressive general vascular disease, it is called upon to do the work of maintaining an increasingly high systemic pressure. Failing blood supply and nutrition are thus coupled with greater demands on myocardial reserve. Under the conditions of hyperpiesia Allbutt said, "neither heart nor vessels are to blame, they are not the sinners but the sinned against, and the heart if defeated, falls in defence of the citadel." It is remarkable, indeed, that the larger vessels of the heart, and not the arterioles, are principally involved (154), and that true myocardial degeneration is comparatively rare (102).

Upon these secondary manifestations of hypertension in heart and vessels, and upon the widespread complications to which in turn the vascular changes give rise, practically the whole art and armament of diagnosis and treatment has been centered. As a problem of the clinic, the consequences rather than the primary affection must remain the focal point of attention until preventive medicine is more successfully applied to controlling hypertension than either human nature or economic and social conditions permit at the present time.

In comparison with the little that is known of the origin of hypertension—hidden in the all but intangible disturbances of the delicate balance between nerve impulses and shiftings of electrolytes in the smooth muscle cell of the arteriole—many methods have served to accumulate a mass of data concerning its structural sequelae. It is salutary to bear in mind, in studying these lesions and using these methods of examination and analysis, that we are investigating the aftermath, and only remotely, and indirectly, the primary problem. We see the damage which has been wrought by a force acting upon the blood vessel, but the nature of this force eludes the eye of the his-

tologist. This issue lies in the domain of function, of physiology and biochemistry.

From the standpoint of the patient, however, it is the duty and responsibility of the physician to determine (1) the presence of vascular changes in the various areas of the body, (2) their extent, and (3) the rate at which they are progressing. On knowing where the danger lies, prophylaxis and treatment hinge. For this purpose (a) the searching analysis of symptoms, and (b) a careful study of physical signs are indispensable. There is nothing in all the elaborate technique of special study which can supplant an adequate history and physical examination. Given this solid foundation and framework, the various refinements of diagnosis then may provide the structure with comfortable furnishings or even with luxurious interior decoration. But laboratory work is doubly expensive if it is substituted for downright clinical thoroughness and blindly directed does not yield the information that is needed. Unnecessary hardship and unwarranted danger are too often incurred when a patient is treated for kidney trouble when the threat is purely cerebral or cardiac. Many repetitions of the urea nitrogen determination will not compensate for overlooking the onset of heart failure. "Unsuitable treatment will often verify a hopeless prognosis."

In his ever practical and helpful book, "The Examination of Patients," Foster wrote that "refined technique is always a product of the individual." But in whatever order or by whatever methods the study of the hypertensive patient is conducted, the aim should be to understand the person as well as the disease.

To this end five main points are worth especial investigation: (1) the patient's heredity; (2) his environment; (3) his manner of living and thinking; (4) the development of symptoms; (5) the objective signs of disease. Few of us are Weir Mitchells in our perceptions and acumen, but "if the observer but observes," the patient reveals unconsciously much that is important toward his complete diagnosis. Systematically, however, the facts are secured by a scheme of procedure which comprises: (1) the history; (2) the examination; and (3) the special clinical and laboratory studies.

Under the heading of symptomatology have been discussed the subjective phenomena. The "cardiac," "cerebral," "renal," or "malignant" types of hypertension are often to be distinguished by inquiry into symptoms. The specific data to be looked for are briefly summarized in the schema (p. 86). There is no more involved and fascinating study than to trace, step by step, the evolution of hypertension as it reveals itself in the life story of a patient. In literature and especially in biography—in the life of

Queen Victoria (Strachey), for example, or of Frederick the Great (Goldsmith)—the familiar signs and symptoms of circulatory disorder trace a thread of interest as genuine as the neurologic and psychiatric shadings in the characters in "Hugh Wynne" or "Westways."

Turning now to the signs of hypertension, the task is that of evaluating the status praesens, in order to be able to infer what has been, and is likely to be, the course of events. And perhaps in no other domain of inner medicine can the condition of the patient and his prognosis be determined more precisely.

HYPERTENSIVE RETINAL DISEASE

Of the various methods of approach, I am inclined to place the study of the eyegrounds first. A consistent use of the ophthalmoscope has given me the conviction that no single method of investigation yields quite so much information, so simply and directly, regarding the nature of the hypertensive process and the patient's outlook and need for treatment.

From the technical standpoint it can be said, parenthetically, that the use of the modern electric descendant of Helmholtz's beautiful instrument is learned quickly, and with a mydriatic where necessary, the fundus can be readily inspected. The interpretation of the usual findings, at least, the medical man soon acquires.

A less important, but practical reason is that ophthalmoscopy serves to divert the attention of the "cardioneurotic" patient and may partly persuade him that to the mind of his physician other matters take precedence over the height of the blood pressure.

In the third place, the ability to evaluate the fundus changes without knowledge of the blood pressure becomes a not unimportant contribution to the clinician's skill in diagnosis and prognosis.

The changes which the ophthalmoscope reveals in the retina in the course of hypertension may be divided into two main groups: First, there are the alterations which are purely vascular in nature. These occur in three stages: (1) spasm of the retinal arterioles, (2) arteriolosclerosis and (3) hemorrhage. In the second group may be placed the lesions which, in contrast, have an inflammatory character, though often there is a vascular component as well. These changes include: (1) edema, retinal and papillary, and (2) those "spots," of varying form, color, size and extent, which are called "exudate." Further, there are proliferative, degenerative and atrophic changes which follow in the wake of insufficient vascular supply, hemorrhage and exudation, but these are secondary, and like coincident changes in the choroid, require no separate discussion.

If not always so-called, the branches of the central artery of the retina are to be regarded as arterioles because of their physiologic reactions. In the sense of Ricker, these precapillary segments may be considered as specialized neuromuscular organs, responding to weak or strong stimuli with dilatation, but to the usual moderate stimuli of environment and milieu with constriction. Hence it comes about that arteriolosclerosis and arteriosclerosis are in all respects—causation, age incidence, histologic structure, anatomic distribution—two separate entities. In the vessels of the retina, then, is seen not senile or decrescent arterial degeneration but an arteriolar response to the active process which underlies hypertonus and hypertension.

Spasm is the first phenomenon of hypertensive nature to be found in the retinal arterioles. Since Pal popularized the conception of vascular crises, observations of temporary constriction in the retinal vessels have not infrequently been reported, for example, in the acute severe hypertension of eclampsia or such paroxysms of high pressure as occur with suprarenal tumors. Mylius (355) has reported these spastic or tetanic contractions in eclamptic women, and has observed waves of constriction, resembling peristalsis, passing along the retinal arterioles. The purely functional nature of the condition is shown by the return of normal tonus when the eclampsia is successfully terminated.

But when the elevation of blood pressure remains high, then a few months later there may be found the second stage in this evolution of hypertensive vascular disease. When the hypertension is at a lower level and its progress more gradual, years instead of months may pass before these same anatomic alterations are established. The end-result, as O'Hare (375, 378) and his coworkers have pointed out, is a characteristic arteriolar sclerosis, almost invariably associated with hypertension and rarely occurring with normal blood pressure even when the larger arteries are markedly sclerosed. Hemorrhage, in the third place, almost always connotes hypertension (268). Blood dyscrasias, infections and traumata are comparatively rare causes.

Therefore, when a patient comes with the history that the family physician found high blood pressure five years before, but promptly "cured" it, and the ophthalmoscope reveals thin tortuous vessels, with irregular lumina and compression at the venous crossings, the conclusion can usually be drawn that the "cure" was temporary, and that hypertension and its effects are a part of the present diagnostic and therapeutic problem. If the patient has high pressure, but the fundi disclose no disease, it is reasonable to assume that the hypertension is of short duration and the prognosis so much the more favorable. If with these well defined vascular changes there is normal or low blood pressure, it is usually evidence of myocardial disease (378).

Finally, if hemorrhage is present in association with this small vessel sclerosis, there is suggested, according to its degree, an exacerbation of a relatively benign process, or the occurrence of hypertension of malignant type.

In the case of C. W., a physician, aged fifty-six, the occurrence of a few retinal hemorrhages ten years ago led to a plan of conservative living, and today his blood pressure is lower, and his general health better, than a decade earlier.

B. H., a woman, aged thirty-seven, sought care because of dizziness and failing vision. The general physical examination disclosed no striking observations. The patient's color was good; the heart was not greatly enlarged. The hemoglobin content was 84 per cent and the red blood cells 4,944,000 per cubic millimeter. Many specimens of urine contained neither albumin nor casts; the specific gravity varied from 1.000 to 1.018, the phthalein output was 50 per cent, the urea nitrogen was 15, creatinine 1.6, the plasma chlorides 450 mg. per 100 cc. of blood. The blood pressure was 280 systolic and 150 diastolic, and there was a great number of fresh hemorrhages. Neither papilledema nor exudation was marked. This patient died in ten weeks of malignant hypertension, and necropsy showed generalized arteriolosclerosis. In the kidneys, which were normal in size, there was no evidence of inflammation.

In other patients the papilledema and cotton wool exudates have been found more prominent in the picture, as in the description of Keith (242) and his co-workers, but in the case of marked vascular disease, they are apparently not inflammatory in nature. Mr. R., for example, aged forty-two, had loss of vision, and his ophthalmologist found so much retinal hemorrhage and exudate that the patient was given six months to live. Under careful management of diet and hygiene, the blood pressure was brought down, the hemorrhage was absorbed, vision returned, and the man led an active life, married and worked steadily for seven years. Eventually, cerebral hemorrhage occurred. Except for the arteriolosclerosis, the retinae at this time were normal. Ten days later, a bilateral papilledema developed, and shortly after, Cheyne-Stokes breathing. Both conditions were relieved by repeated lumbar punctures. There developed during the last two months of life a terminal pyelitis, and fresh exudate appeared in the retinas, but no hemorrhage. A low grade uremia, with twitching and slight convulsions, was present during the few days preceding death, but the blood chemical examination on the day before death showed no retention of nitrogen.

Turning now, from this example of a transition, to the purely inflamma-

tory group of retinal lesions, edema, in the absence of arteriolar disease, will be found almost always associated with edema elsewhere in the body. In the recent case of a man, aged thirty-two, the victim of acute glomerular nephritis, with a complicating pericarditis, there were marked pallor and general anasarca. Retinal edema was the only ophthalmologic sign. The blood pressure was not elevated, and the patient died with uremic convulsions eighteen hours after the consultation.

If the blood pressure becomes elevated, which is the rule if acute nephritis is not successfully dealt with and subacute or chronic nephritis develops, there are found in the eyeground the soft white or buffy spots and patches, without the arteriolosclerosis, for the development of which time and the functional strain of continued hypertension are required. V. W., a man, aged forty-six, who had added various infections, especially dental, to chronic abuse of alcohol, came into the hospital in uremic coma. He was pale and edematous; the blood pressure was 200 mm. systolic and 130 mm. diastolic. The ophthalmoscope showed slight edema, some vascular constriction and irregularity, no hemorrhage, but extensive patches of soft white exudate. Six months later these last had contracted, in part been absorbed, and were much sharper and brighter.

What may be called pure clinical types of hypertensive retinal disease have now been pointed out, in one group of which arteriolar spasm, arteriolar sclerosis and hemorrhage are the stages of development in a progressive vascular condition, while in a second group edema and exudate appear, both often before actual vascular disease can be detected, but the latter never, as a rule, without the presence of hypertension. Much more common than the pure types, of course, in patients who are seen comparatively late in the course of hypertension, are clinical pictures in which exudate and hemorrhage, edema, proliferation of connective tissue and of pigment and degenerative and atrophic changes are so intermingled that interpretation of type is somewhat difficult. In the exudation which accompanies severe vascular disease, it is certain, as Wagener's (485) histologic studies have conclusively shown, that the process is not inflammatory.

In a study of the retinal vessels in 2000 unselected patients on the general medical services of two hospitals, the Friedenwalds (165) established six groups of cases. Hypertension without retinal arteriosclerosis was present in patients with essential hypertension, acute nephritis, mild toxemias of pregnancy, increased intracranial pressure, hyperthyroidism with high systolic pressure, and high pressure stasis. A group with "chronic nephritis" showed retinal arteriolar sclerosis, which, the authors point out, can first be seen in the macula, where the vessels have an internal diameter of 10

to 15 microns. Retinal arteriosclerosis without hypertension and with hypertension and associated with syphilis and local disease made up the other four classes. In the Friedenwalds' first group it appears probable that the elevation of blood pressure had not been of long duration. In patients with heart disease who have had hypertension, Yater and Wagener (502) found that 90 per cent show some degree of retinal arteriosclerosis, while 96 per cent of those whose heart disease is due solely to hypertension show retinal changes. Retinal arteriosclerosis is divided into two well defined hypertension and senile types (8, 501).

THE STUDY OF BLOOD PRESSURE

While it must frequently happen that "he who comes to the physician's office a well man, departs thence under the burden of a column of mercury," I believe that, with few exceptions, the patient should have knowledge of his blood pressure. The statement, tempered with a reasonable optimism, of what hypertension means and what it does not mean, need not convey the sense of overwhelming catastrophe that it sometimes brings. As Osler (385) said, hypertension has its advantages as well as disadvantages. Like the trace of albumin in the urine of the man of fifty, it is a warning to be heeded and profited by.

Such knowledge is not only essential to intelligent coöperation, but it does the patient more real psychologic harm to refuse to let him know the reading than to tell him frankly. I have seen a physician subtract forty points from his determination supposedly for the benefit of the patient without being convinced that actually this deception favored the man's well being.

It is, however, a part of the art and technique of studying blood pressure to make it a simple matter of routine and not the climax of the examination. Sometimes the reading may be omitted in routine examination with psychologic profit, though occasionally it is possible thus to offend "sensitized" ladies who have come to live by and for their blood pressure. One such person had purchased her own instrument for ready reference. She recalls to mind Sir Risdon Bennett's account (58) of a woman of Bright's generation, probably hypertensive, who upon dying of congestive failure at the age of forty-two, was found to have healthy kidneys and a heart weighing 23 ounces and free from valvular disease. Besides these, she left a copious diary in which she had put down every item of treatment from all her five doctors over a period of twenty-seven years. In brief, she had been cupped and bled 962 times, and had lost 9506 ounces of blood irrespective of that extracted by 593 leeches.

At the critical moment of the determination Kilgore (243a) suggests the

technical refinement of an inquiry concerning the state of the bowels. Other neutral questions may be substituted to distract the patient's mind from the procedure. The manometer should lie outside the patient's line of vision. Nor should the arm be kept constricted while the auscultator searches for his stethoscope or the artery. To avoid a secondary reflex rise, the reading should be taken expeditiously (203).

Thus, a combination of tact and technique during the examination and in the interpretation of findings will in most cases preserve the even-mindedness of the patient, and permit intelligent information without the development either of a phobia or excessive interest. The very real value of the knowledge of the blood pressure to patient and physician alike must be safeguarded by an attitude which combines both frankness and discrimination.

Often we err, I believe, in not insisting that our patients have the information which will enable them to decide issues that arise when medical counsel is not convenient or available. When a man aged forty-two years, a lawyer, with hypertension and a defective myocardium, asked my advice regarding a quiet vacation at his old home in the middle West, I gave my assent. Frightened at the outset by paroxysms of nocturnal dyspnea, he had lightened his load and had done well for six months. He slept well, had no dyspnea, and took pride in his ability to play nine holes of golf in 45 strokes. The day before he went away, he took a new case, spent most of the night in preparation, tried the suit in the morning, and left town in the afternoon. In the sleeper he was overtaken by paroxysmal dyspnea and after unsatisfactory results from treatment he died a few days later.

VARIABILITY OF BLOOD PRESSURE

The two intrinsic qualities of blood pressure which chiefly interest the clinician are (1) its height and (2) its variability. These are closely, but inversely, related. The higher the level of hypertension, the less labile. This is the distinction between functional disorder and anatomic disease. Variability indicates an earlier stage and brighter possibilities of treatment. Fixation and irreversibility foredoom therapeutic efforts.

This lability of blood pressure has made the study of its hourly, daily, seasonal variations of interest and value. Spring and autumn, Kaufmann (238) states from mid-Germany, appear to be critical times for patients with hypertension. Symptoms increase, the incidence of apoplexy rises. Kylin (261), as evidence of a common etiology and nature, finds the same seasonal periodicity in respect to gastric ulcer and vegetative neurosis. Are inner secretory and alterations in intermediary metabolism the cause of these seasonal changes seen in the altered reaction of the blood (464) and the morphology of the capillaries?

In Chicago Bundesen (93) investigated the mortality records from 1924 to April, 1926, and found that the seasonal factor brought an increase in sudden deaths from organic heart disease, cerebral hemorrhage, and chronic nephritis when the temperature was low and a low death rate from these causes when the temperature was high. Barometric pressure variations, contrary to observations in England, showed no correlation.

In New York State Kinney (247) called attention to the frequency of apoplexy when, in winter, cold dry weather followed a warm humid spell, and again in summer, when a hot wave swept over the country. Kinney believes from his experience that many persons show higher tension during hot weather. He finds that many patients are much more comfortable at an elevation of 1500 feet than at sea level. A man now under my observation believes that in Florida his winter comfort is greater than in Vermont, a statement which few would dispute. In another patient, a woman with hypertension and sclerosis, the anginal attacks were greatly aggravated by cold weather. When a brisk wind was sweeping the street in winter, it was necessary for her to walk backwards in order to avoid a continuous status anginosus.

Fluctuations in blood pressure during sleep have long had the attention of workers. The rather precipitate fall that occurs during the first hours suggests strongly that the hypertensive patient will profit from regular habits and sufficiency of sleep. High pressure does not always fall however, and unpleasant dreams have been shown (301) to produce sharp rises. Campbell and Blankenhorn's (97) recent work sums up the facts regarding the effect of sleep on hypertension: the 33 patients whom they studied could be divided into two groups. Those with the greater evidence of disease showed a sustained sleeping pressure, while a fall in pressure during sleep occurred only in those whose initial pressure and vascular changes indicated less advanced hypertension.

The observations of diurnal variation in blood pressure led Kylin (261) to place patients with hypertension in four groups: (1) Those with definite hypertension which sinks to normal (120 to 130 mm.) with rest in bed, but may show a daily rise, usually in the evening, of 20 to 40 points. (2) Patients with less pronounced fall, so that evening blood pressure definitely exceeds the normal (160 to 165 mm.). (3) Both morning and evening values are abnormal (150 to 190 mm.) while diastolic pressure remains at 80 to 90 mm. Very wide fluctuations may occur—70 mm. in twelve hours and as much as 120 mm. in the course of a week. (4) Finally, those patients in whom the pressure at no time descends to normal. From these findings, which Fahrenkamp (147), C. Müller (349), Sigler (450) among others con-

firm, Kylin is led to state that essential hypertension is "less an increase of the blood pressure than a lability." By contrast, the blood pressure readings of acute glomerulonephritis show a characteristic stability at a much lower level.

Diehl (113) has reported morning and evening studies of blood pressure in 100 healthy male students over a period of six days. A reading taken between rising and breakfast gave a mean of 115 mm., that made at the close of the day's activities before dinner, 124 mm. An average total range of approximately 30 mm. was considered to be within the limits of "normal" variation. Since mathematical treatment of these results does not establish a positive correlation between height of blood pressure and its variability, Diehl is inclined to doubt that transient elevations in young persons really represent the first stages of a persistent hypertension and the validity of the significance the clinician usually attaches to these fluctuations is questioned. No relation between the level of pressure and its variability was found by Diehl and Lees in studying blood pressure at five-minute intervals for an hour. In this group of 100 normal freshmen, the mean systolic pressure was approximately 111 mm. A few months before, at entrance, it was 117.5 mm., indicating a factor of apprehension and nervousness and suggesting that such examinations do not represent the true blood pressure values. In this second series, there is a decrease in the first three readings, and a less definite fall until the eighth and lowest reading is reached. In 84 per cent, the highest pressures were found in the first three readings, after the eighth reading in only 3 per cent. One highly emotional boy showed a gradual rise from 118 to 160 mm. in fifty-five minutes.

The spontaneous changes in blood pressure have also been studied in detail by O'Hare (372), Mosenthal (344) and many others.

THE HEIGHT OF BLOOD PRESSURE

With full recognition of the fact that in most patients he is studying neither a basal blood pressure (4) nor one which ever ceases to rise and fall in response to many sorts of stimuli, the clinician must draw deductions from observations that at best are only partly controlled. It is not often possible in office or even hospital practice to establish the base line that a rigidly scientific experiment would demand before the testing of a drug, for example, can be begun. Time, money and human impatience forbid. The doctor must treat the patient, and the experiment takes the best place it can get.

Nevertheless, I am thoroughly convinced that in the majority of patients it is possible to approximate, if not the basal pressure, the usual pressure

level of ordinary daily life, and this latter, after all, carries the greater practical significance. Even at the first consultation, an attitude of reassurance during the taking of the history relieves mental tension at the same time that physical factors are subsiding with rest, and comparisons of blood pressure at the beginning and at the end of the physical examination, or between the level in recumbency and that standing are useful methods of control. Rowntree allows three days of rest in bed, with no medication, and blood pressure taken thrice daily, to establish a base line (10).

In respect to the level of the blood pressure, hypertension falls into three main groups. The first, and the largest group, shows elevation of the systolic pressure and a normal diastolic pressure. In this group are the younger people, with early or mild hypertension. In the second group, the systolic and diastolic pressures are both elevated, the patients are older and the disease is more advanced. In a series of 2568 cases, Frost (167) found the incidence of the first group to be 51.7 per cent, and of the second group 44.4 per cent. A third group, 3.9 per cent, showed a high diastolic pressure and a relatively low systolic level, and occurs late. The characteristic progression of primary hypertension is evident.

It has been suggested that increased cardiac output causes the rise of systolic pressure, while diastolic hypertension is dependent on the factor of increased peripheral resistance (161). Hence the futility of treating all cases of hypertension as if of common origin. In the case of the high systolic pressure which is seen in hyperthyroidism or in aortic insufficiency, the overactivity of the left ventricle is definitely responsible. Pulse pressure is high, diastolic pressure may be zero. These instances, however, are not primary or genuine hypertension, and as Mosenthal has pointed out in regard to the high pressure in hyperthyroidism, the progressive course may be absent.

Neither the velocity of the blood (204, 493), nor the minute volume of the heart (94), rise above normal in chronic hypertension which is uncomplicated by failing circulation. Even when peripheral resistance is shown by heightened capillary tension, the level of diastolic pressure rises slowly and insidiously and often has not reached a pathological degree. Eventually, however, the elevated diastolic pressure, because it represents a constant strain on heart and vessels, becomes as important as the systolic tension, if not of greater significance, in determining the prognosis. A diastolic level of 120 mm. is often not borne more than two years, and one of 150 mm. ordinarily conveys the prospect of death within a few months (211).

The effect of atherosclerosis of the aorta and larger vessels on blood pressure has been investigated by Fineberg (151). In 237 cases of hyperten-

sion, 66 or 28 per cent had high systolic and relatively low diastolic pressures. In the age group between forty and fifty years, the incidence was 9 per cent. It increased to 58 per cent in those patients who were eighty years or more. In the majority, the usual symptoms of hypertension—headache, dizziness, throbbing in the head—were absent and cardiovascular symptoms were rare. Generalized arteriosclerosis was commonly found both in clinical and pathological examination. The course was benign and prolonged. Fineberg believes that the systolic hypertension of persons with large vessel sclerosis deserves to be placed in a special group.

There is another not unfavorable association of hypertension and valvular heart disease. Levine and Fulton (283) suggest that the tendency of the left ventricle to dilate under the strain of aortic hypertension is opposed by the mitral stenosis, while extreme narrowing of the mitral ring is prevented by the enlarged ventricle. At any rate, of 762 patients with mitral stenosis, 159 were over forty-five years, and 58 per cent of these had a systolic pressure of 150 mm. or more and a diastolic pressure of 90 mm. or more. Of 135 patients with mitral stenosis analyzed by Boas and Fineberg (76), 29 per cent had hypertension, and only 5 persons were under forty years. Cardiac failure was not a factor. Of 60 patients with aortic insufficiency, 27 per cent had pressures over 170 systolic and 90 diastolic. Of 75 patients with combined lesions, 8 per cent had hypertension.

Diastolic hypertension with increased basal metabolic rate has been set apart as another special syndrome by Boas and Shapiro (76a). It is to be distinguished from exopthalmic goiter by lack of eye signs, struma, tremor and asthenia. Thyroidectomy in 3 of their patients brought no relief. The clinical features in 10 cases were the hypertension, especially diastolic, tachycardia, loss of weight, pigmentation of the skin. The elevated basal rate in one case was plus 86 per cent.

THE HEART

In a physician, aged fifty-seven years, whose blood pressure has been elevated since he was thirty, and ten years ago was 170/110, I was unable by palpation or percussion to detect evidence of cardiac enlargement. On the other hand, in a laborer of forty-five years, who has noticed dyspnea only a few weeks, the point of maximal impulse and the left border of the area of cardiac dulness lie in the mid-axillary line, and the right border extends 5 or 6 cm. beyond the mid-sternal line.

The heart of hypertension ranks with the cor bovis of aortic insufficiency and of adhesive pericarditis in exhibiting extreme degrees of excentric cardiac hypertrophy. Yet for years, particularly in the patient with ptotic

habitus, the heart may show only a concentric form of hypertrophy which defies discovery by physical examination. Quality of tissue is as likely to play a part here as it does in the rest of the vascular system. So also does the height of systolic, and perhaps even more, diastolic pressure, since the importance of diastolic level in maintaining adequate coronary blood flow has been proved by Smith (453) and others. The contention that low diastolic pressure leads predominately to "cardiac" death and high diastolic pressure to "cerebral" death is not, however, borne out with any degree of consistency (151). In malignant hypertension, where the level of pressures is highest, death is often due not to weakness of a particular organ, but apparently to the diffuse vascular disturbances simultaneously occurring in many parts of the body (241). A third factor, undoubtedly, in producing hypertrophy of the heart is physical strain; freedom from the necessity of heavy labor is one of the first requirements of the patient who must safeguard his diminished cardiac reserve (133).

The earliest evidence of the heart's compensatory response to hypertension is given by fluoroscopy, the orthodiagram (137), or the 6-foot film, in the form of the bulging elliptical contour of the upper border of the left ventricle (267, 353). This change precedes transverse broadening with enlargement of the shadow downward and outward (277).

At the same time, the aorta reacts to the strain of continued high pressure with dilatation, elongation and displacement, best seen in the oblique diameters on fluoroscopy, but also suggested, at least as far as the widening of the ascending portion is concerned, by extension of dulness on percussion beyond the normal limits of 6 or 7 cm. The upward lift may be seen and felt as a pulsation in the episternal notch. The pulsation of the subclavian arteries sometimes becomes so prominent in thin hypertensives that aneurysm is suggested. Jugular distension may result from external pressure on the vein.

Besides the increase in size, the two other cardinal signs of the heart working against increased resistance are the heaving apex thrust and the ringing, accentuated aortic second sound. Not always are these signs frank. Fat and emphysema make examination difficult and the findings obscure.

Lange (267) calls attention, by way of contrast, to the broad low heart of arteriosclerosis with no increase in weight unless valvular disease is present or hypertension supervenes. The transverse diameter is greater than the long diameter. The aorta is broad, dense, and short. Cardiac insufficiency is almost always present—of 341 cases without hypertension, in only 26 were symptoms absent. Dyspnea occurs on effort, with little increase in pulse

rate or blood pressure. Though the hypertensive heart presents left ventricular hypertrophy, its long diameter is greater than the transverse. The aorta is heightened and displaced. On exertion there is a marked increase in pulse and blood pressure.

With the onset of cardiac insufficiency, there appears a great variety of signs which need only be touched upon here.

The apical systolic murmur of relative mitral insufficiency is the most common finding in the failing heart of hypertension. Fahr (142) states that 80 per cent of the cases sooner or later show this evidence of dilatation. Paullin (393) found the sign in 26 per cent. The murmur simulates, but is not the evidence of, valvular disease. It arises because the enlargement of the left ventricle stretches the mitral ring and the valves become imcompetent; it is the consequence of heart failure and not its cause. With restoration of cardiac compensation, the murmur may disappear. When the course of disease is unfavorable, the relative insufficiency allows the regurgitant blood to dilate the left auricle and thereby augment the state of congestive failure.

Systolic murmurs at the aortic area are somewhat less common, and less significant. Paullin found them in 5.8 per cent of his patients. They cannot be interpreted as evidence of stenosis unless accompanied by a thrill. As a possible sign of changes in the root of the aorta the systolic murmur at the base carries most weight; sclerosis of the valves is less often present.

The rather rare diastolic murmur arising in the aortic area in the presence of high pressure is an interesting finding. In a hypertensive patient, who died of the unusual complication of dissecting aneurysm of the aorta, it was possible to show that the high pitched blowing diastolic murmur at the base and transmitted down the left border of the sternum and well heard at the apex, was purely functional (170). The valves were not sclerotic and there were few intimal lesions in the aorta; dilatation, however, was well marked and besides causing the relative insufficiency of the aortic ring was perhaps directly responsible for the primary internal tear from which the dissection took origin. The presence of such a murmur, of course, necessitates consideration of syphilitic, or rheumatic infection, arteriosclerosis and anemia as possible etiological factors.

The heart sounds in hypertension are often clear and loud, as might be expected of muscle and valves capable of maintaining high pressure over years (102). Distant and muffled sounds may or may not indicate myocardial change, intervening tissues again altering physical findings. When the sounds change in quality under observation, it is highly significant of pathological alteration. The detection of reduplication or splitting of the

first sound points to gallop rhythm (330) and carries a grave prognosis. The rarer condition of intraventricular block has been diagnosed clinically by King (246) from a bifid apex thrust which is visible and palpable, and accompanied by feeble sounds. Reduplication of the second sound in this condition was striking but not constant.

Departures from normal sinus rhythm are common in the hypertensive heart. Premature beats may occur as a sign of myocardial irritability in the early stage when fluctuations of blood pressure are so pronounced. Under the strain of constantly altering peripheral resistance, the compensatory cardiac mechanisms tire—in Kaufmann's words, "the vessels give the heart no chance to rest." Later in the course of hypertensive disease, premature contractions are to be regarded more seriously—particularly if they increase in frequency with exercise or if they arise from a number of foci—as evidence of structural disease.

As a late manifestation of hypertensive heart failure, auricular fibrillation is a condition which, like coronary thrombosis and myocardial infarction (168, 197), may greatly lower the blood pressure and mask a "virtual" hypertention (378). Broadbent early pointed this out (86). In these patients the two important diagnostic criteria are the size of the heart and the appearance of the retinal arterioles. Both fibrillation and flutter of the auricles occur, however, without demonstrable pathological basis and may be well borne for long periods.

Tachycardia in hypertension has been studied by Mannaberg (312) who in 241 patients found it present in 43 per cent. The basal metabolic rate was commonly above normal.

Bradycardia has been said to elevate blood pressure by increasing cardiac output. In a man of eighty years, just studied, with a ventricular rate of 39 beats per minute, and the electrocardiographic evidence of complete heart block, the blood pressure varied from 190/100 to 160/90. This pressure apparently however, antedated the block, though retinal changes were not pronounced and the heart was only moderately enlarged.

Pulsus alternans occupies a position of prognostic importance in the terminal stages of the hypertensive heart, may be detected by palpation when there is a marked weakness of the alternate beats, but is better recognized by the blood pressure variation either on auscultation or with the graphic methods of registration (51, 404).

The functional reactivity of the cardio-vascular system and its ability to endure the strain has been studied by Frost (167) by means of the "cardio-respiratory test." The changes in systolic blood pressure are determined during variations in intrapulmonic pressure induced by deep inspira-

tion and expiration and by the further steps of forced expiration and inspiration measured by pressure gauge and spirometer. Four types of reaction, normal, hyperactive, hypoactive and hypertensive, are found. In a series of 1539 applicants for life insurance, 58.3 per cent of those with heart murmurs, 41 per cent of those with hypertension ("few with systolic pressure exceeding 150 mm."), 71.9 per cent of persons with low blood pressure, 69.9 per cent of persons with irregular pulse, have been accepted as desirable risks. Such applicants, Frost states, and others with enlarged heart, underweight and obesity, goiter and tachycardia, would have been refused favorable action in the past.

Until myocardial changes result from the later vascular complications, the electrocardiogram in patients with hypertension shows no distinctive changes. Ziskin (504) has recently studied 100 patients with high pressure and has found that not even left ventricular predominance is constant. It was present in 44 per cent, but neither the height of the blood pressure nor the degree of left ventricular hypertrophy appeared to be determining factors. The x-ray plate in 33 of these patients showed no cardiac enlargement, findings which coincide with those of Rosselet and Mahaim (429).

As heart changes progress, however, the electrocardiographic records often offer the first objective evidence of the site and extent of lesion and of the physiological mechanisms involved, and the presence or absence of significant variations in the conduction time, and QRS and T-waves have a most important bearing on prognosis and treatment.

RENAL FUNCTION

In 97.2 per cent of patients with the vascular changes resulting from hypertension, Harpuder (188) found some disturbance of renal function. There was cylindruria in 18.9 per cent, albuminuria in 53.3 per cent. Tests of the ability of the kidney to dilute and concentrate urine and to excrete salt and urea brought the final percentage of disability.

Most delicate of all tests is the comparison of blood urea with the level of urea in the urine. With these tests Lian and Barrieu (286) found renal function disturbed in 90 per cent of patients with permanent hypertension. In healthy persons with one kidney Foster (162) found the MacLean index slightly below normal.

On the other hand, Lange (267) found in pure hypertension, his patients selected before vascular disease had had time to develop, that kidney function was even greater than normal. Müller and Hübener (352) had no difficulty in collecting 50 patients with primary hypertension who showed no retention of nitrogen and normal excretion of water, sodium chloride and

urea. No relation has been found between the degree of hypertension and that of renal insufficiency. Little correlation exists between the results of the more refined tests of kidney function and prognosis. More than two-thirds of the kidney substance must be removed before insufficiency ensues. Renal function remains unchanged during the course of benign hypertension, and if often little affected in malignant hypertension. Relatively few patients with hypertension die of uremia, with which it has become clear that neither urea nor other forms of nitrogen retention nor high pressure need have anything to do. Death after typical convulsions has been mentioned in the case of a young man with subacute glomerulonephritis of four months' duration and the terminal complications of fibrinous pericarditis, oliguria, edema, and uremia. The blood pressure did not exceed 120/80.

The most valuable renal functional tests are the simplest. In this country the three objects of study are commonly: (1) the excretion of phenolsulphonephthalein, (2) the fixation of specific gravity (in two hourly specimens throughout the day, compared with the amount and specific gravity of the twelve-hour night urine, (3) nitrogen retention in the blood, as shown by urea or non-protein nitrogen.

Experience in the study and treatment of ambulant patients with hypertension soon is convincing that the methods which yield quantitative information regarding the state of hospital patients with advanced lesions give little positive help in the earlier stages. The results are practically always within normal limits. Against the more delicate tests are the objections that they are difficult or time consuming and only exceptionally yield data which have a bearing on the patient's course or treatment.

This overshadowing of renal function by more important conditions is shown by the course of the following patient: M. K., aged fifty-three, a German housewife, complained of flushes, palpitation and shortness of breath of a year's duration.

A brother had died suddenly at fifty-six. The patient's pressure was found high during pneumonia at fifty. The menopause came at forty-eight and the patient still has flushes night and day. Her head feels dull and she gets up at night in order to "change the circulation." After ten minutes, she can go back to bed and sleep. There is nocturia once. There is no anginal pain, but an occasional numbness under the left breast. There are no visual disturbances.

Physical examination shows that the patient is obese and red-faced. The blood pressure is 210/130, pulse 96 to 100, regular in rhythm. The arteries are barely palpable. No retinal hemorrhage is found. The heart is enlarged 10.5 cm. to the left.

The urine contained a faint trace of albumin, no sugar. The urea nitrogen was 12 mgm., the uric acid 5 mgm. per 100 cc. The two-hour specimens of urine, with an intake of 1500 cc. of fluid blood showed a variation of specific gravity from 1.015 to 1.023. The total day specimen was 555, specific gravity 1.019. The night urine was 800 cc., specific gravity 1.012.

During three months of observation, and the use of digitalis, sodium bromide and ovarian gland, the blood pressure fell to 145/85 and symptoms were relieved.

One year later, the patient returned with the complaint of being "tired all the time." The specific gravity of the urine was now fixed between 1.015 and 1.018. The day urine totalled 1155 cc., specific gravity 1.016. The night urine was 925 cc., specific gravity 1.014. An electrocardiogram revealed bundle branch block. The patient died suddenly eight months later.

In this patient there was retention of uric acid, and while the fixation test indicated moderate impairment of renal function, which had become more marked the following year, death was from myocardial disease.

The dilution and concentration tests and determination of the excretion of measured amounts of sodium chloride and urea continue to be the popular standard methods in European clinics. The first two tests can be performed conveniently in a twelve-hour period, as follows:

At 7.30 a. m., the fasting patient after voiding is given 1500 cc. of fluid. The rapidity and amount of excretion and the variation in specific gravity is measured by collecting the urine hourly for four hours, or even half hourly during the first two hours. A dry lunch follows and no liquid is given during the rest of the day: conditions under which the kidneys may be expected to show their power of concentration. Normal kidneys and those of patients with hypertension without renal disease show a rapid output of urine equalling or surpassing the intake even in the first two hours. Variability of specific gravity is wide. In contracted kidney the excretion is delayed, specific gravity is low and fixed and the hyposthenuria is prolonged through or beyond the period of the fluid intake.

The contrast between these renal extremes in hypertension is illustrated by these two examples (table 5), from Munk.

Bolliger (77) has compared the two-hour excretion of sodium thiosulphate and sodium iodide with that of phenolsulphonephthalein in the two-hour test. The three substances were injected together intravenously in dogs, before and after the production of experimental nephritis. His observations, in opposition to those of Nyiri, showed that great variations in the output of the iodide took place without definite relation to the

amount of kidney disease. Sodium thiosulphate, however, was found to be a quantitative test for experimental renal insufficiency, somewhat more accurate than 'phthalein and perhaps better adapted to detect slight lesions in the kidneys.

Bolliger cites Nyiri's and Eskelund's gratifying results with its clinical use. In contrast with 60 to 70 per cent phenolsulphonephthalein output, 30 to 40 per cent excretion of sodium thiosulphate is normal.

TABLE 5

Dilution and concentration test

TIME	HYPERTENSION WITHOUT RENAL DISEASE (BLOOD PRESSURE 185 MM.; NON-PROTEIN NITROGEN 32 MGM. PER CENT)		HYPERTENSION AND PRIMARY CONTRACTED KIDNEY (BLOOD PRESSURE 205 MM.; NON-PROTEIN NITROGEN 125 MGM. PER CENT)	
	Amount of urine	Specific gravity of urine	Amount of urine	Specific gravity of urine
7.30 a.m.	652	1.020	1880	1.006
	1500 cc. fluid by mouth		1500 cc. fluid by mouth	
8.00 a.m.	131	1.008	120	1.003
8.30 a.m.	235	1.000	240	1.001
9.00 a.m.	600	1.000	212	1.002
9.30 a.m.	504	1.000	320	1.000
10.00 a.m.	296	1.001	100	1.004
11.00 a.m.	59	1.009	58	1.005
12.00 m.	38	1.010	140	1.010
2.00 p.m.	54	1.018	122	1.010
4.00 p.m.	46	1.021	100	1.009
6.00 p.m.	24	1.021	150	1.010
8.00 p.m.	48	1.021	40	1.010
8.00 a.m.	162	1.028	468	1.006

The determination of the excretion of urea (244), chloride (15), uric acid, creatinin and guanidine (309, 310, 370) in the urine or their retention in the blood following the ingestion of measured amounts is aimed at detecting specific disturbances in kidney function. It is not certain that such studies of metabolites really yield more information than does the use of the foreign phenolsulphonephthalein.

From the clinical point of view, one must agree with Munk (353) that in the diagnosis and prognosis of hypertension tests of renal function have been overprized. After a careful weighing of easily obtainable clinical facts and the simpler methods of analysis, it is time to ask whether and what a functional study of the kidneys would contribute to the understanding of

the pathological process. In most cases the goal can be reached without the exhaustive study of renal function which is sometimes felt necessary, while weaker links in the chain of hypertension and its complications are ignored.

The extent and the nature of the renal lesion, Addis (5) maintains, must be answered more definitely and specifically than clinical observation and tests of renal function have so far done. Neither a tendency toward "fixation" of specific gravity of the urine, a diminished phenolsulphonephthalein output, nor a rise in non-protein nitrogen, are anything, he states, but "qualitative answers even though given in numerical terms, and do not satisfy the precision which the question demands." . . . . "What we want is a clinical method which will give an insight into the nature of the predominant morphological changes as they occur in the kidney from the very beginning of the process, from month to month, and from year to year, throughout the whole course of the development of the renal lesion."

Under the two essential conditions of sufficient concentration and sufficient acidity of the urine in order to prevent cellular solution, Addis has studied the rates of excretion of casts, red blood cells, white blood cells, epithelial cells and protein. Counts made on 74 apparently healthy medical students revealed facts of much interest. The average excretion was studied after the subject abstained from fluid during the day and collected the night urine over the customary twelve-hour period, this method nearly always fulfilling the required conditions except where only a remnant of functioning kidney tissue is present.

The rate of excretion of casts varied from 0 to 4270 in the twelve-hour period, with an average of 1040; of red blood cells from 0 to 425,000, with an average of 65,750; and of white blood cells from 32,400 to about 1,000,000, with an average of 322,550. The excretion of 30 mgm. of protein in twelve hours was found to be the upper limit in normal subjects. Renal disease is present, therefore, when the protein in the urine exceeds 30 mgm. in the twelve hours, and the white blood cells number more than 5000. The ratio of rate of urea excretion in hourly periods to the blood urea concentration was also found "under attainable conditions an approximate measure of the mass of renal tissue."

The evidence accumulated by Addis and his co-workers, correlates hematuria and glomerular inflammation, increased excretion of epithelial cells with tubular degeneration, and a continuing slight excess of casts, protein and cells in the urine with probable vascular changes in the kidney. The course of the disease, the intermingling of types, the diminution of functioning renal tissue and the appearance of renal failure are measured thus in terms of objective quantitative data.

A schema for the clinical study of hypertension

I. Chief complaint: The patient's own account of his present symptoms.

II. Family history: Condition of health, or cause of death, and the longevity of each immediate relative. Inquiry as to inherited physical and mental traits.

III. Past history: Usually merging, in chronic disease, with present illness.

Infections, especially those causing kidney disease: tonsillitis, scarlet, typhoid, pneumonia.

Review of systems, with especial attention to:

Cerebral symptoms: Headache, migraine, dizziness, irritability, visual disorders, insomnia, mental changes.

Cardiac symptoms: Dyspnea, including the response to exertion, e.g., stair climbing; pain, palpitation, cough, edema, weakness.

Renal symptoms: Nocturia, frequency and amount of urination, pallor.

Digestive: Constipation, fullness, pain etc.

Joints: Pain, stiffness.

Weight: Gain or loss, and rate.

Diet: Use of meat, salt, carbohydrate, alcohol, tobacco, coffee, water.

Sleep: Amount, interruptions (urination, dyspnea).

Exercise, recreation, relaxation; home life; character and conditions of work. Sexual habits.

IV. Present illness: The appearance or the progress of symptoms.

V. Physical examination:

General appearance. Height, weight, build, color and condition of skin.

Ophthalmoscopic examination:

Pupillary reaction.

Retinae (provided media are clear):

Color.

Arterioles (especially of macula):

Thinning and irregularity.

Tortuosity.

Compression of veins.

Hemorrhage (fresh, old, shape, location).

"Exudation": Color, size, shape, border (sharp, fuzzy).

Edema:

Retinal.

Papillary.

Teeth, tonsils, sinuses.

Blood pressure: Pulse rate, rhythm, volume, tension, vessel wall.

Heart examination:

Pulsations in neck, at base and apex.

Thrusts, impulses, accentuated sounds.

Cardiac and aortic dulness.

Sounds, murmurs, gallop rhythm.

Functional tests (exercise, changes in posture, "cardiorespiratory," vital capacity).

Lungs: Expansion, resonance, râles, especially basal.

Abdomen: Enlargement of liver, free fluid.

Knee jerks, edema, accessible arteries.

Routine laboratory examination:

Urine: Specific gravity, reaction, albumin, glucose, (cells, red, white and epithelial; casts).

VI. Special clinical study (where indicated for exactness or completeness of diagnosis).

Fluoroscopy: Size and position of heart; contractility; dilatation and displacement of aorta (expecially in oblique diameters of chest); excursion of diaphragm and lungs.

Electrocardiography: State of heart muscle, detection or elimination of preclinical myocardial disease; diagnosis of irregularities of rhythm; prognostic data in advanced disease.

Capillary microscopy and manometry.

Venous pressure (estimation of myocardial failure, Eyster).

Adrenalin reaction (primary or secondary rises in blood pressure).

Special laboratory study. (for precise functional diagnosis).

Urine. Quantitative estimation of protein, red and white blood cells and casts in twelve-hour specimen (Addis).

Fixation of specific gravity: two hourly specimens 8.00 a.m. to 8 p.m., total night urine to 8.00 a.m. (Mosenthal).

Phenolsulphonephthalein excretion (also sodium thiosulphate).

Dilution and concentration tests: Excretion, following 1500 cc. fluid, four-hour period; excretion on dry diet, eight-hour period.

Excretion of solids: Salt, urea, creatinin, guanidine.

Blood:

Hemoglobin, red blood cells, white blood cells, (sedimentation).

Volume, velocity.

Nitrogenous bodies: Non-protein nitrogen, urea, uric acid, creatinin, guanidine, polypeptide nitrogen, amino-acids.

Chlorides in blood and plasma.

Sugar.

Cholesterol.

Calcium, potassium.

Epinephrine content (biological assay).

Hydrogen-ion concentration.

Protein partition (refractometry)

Wassermann and Kahn reactions.

Spinal fluid:

Pressure (blood pressure response).

Sugar content.

Biopsy: Histological study of arterioles of pectoralis major muscle.

CHAPTER IX

Prognosis

The future of patients with arterial hypertension, as a group, falls within limits so definite in respect to longevity and mode of death as to have almost the force of natural law. The prognostic significance of high blood pressure has been firmly established by the data of life insurance medicine. These facts the physician, in dealing with the individual patient, cannot afford to ignore.

Almost the first and mildest statement that the statistics of life insurance present is that a consistent elevation of 10 or 15 mm. in the systolic pressure, or hardly more than 10 per cent, above the average for the age, increases by 36 per cent the expected death rate (156). It follows that the term "benign" applied to hypertension has only a relative and distinctly limited meaning. The "critical level" of systolic pressure is not, therefore, 170 or 200 mm. It is any elevation persistently higher than the standards of blood pressure arrived at through the examination of a quarter million or more healthy American applicants for life insurance (218).

Grounds for reasonable optimism in the prognosis of the person with hypertension are to be found, on the other hand, in certain individual factors. First, there is the great variation from one patient to another in the response to the burden of high pressure. Secondly, and chiefly, the early recognition of hypertension and the opportunity thereby given to analyze and alter its underlying and complicating conditions provide the way for rational measures of prophylaxis and treatment.

These two contrasting points of view are thus set forth by Symonds (468):

"Probably life insurance and general medicine will never regard blood pressures in the same light. Life insurance sees only patients who are healthy, or at least think they are. Even the highest pressure of fat, elderly persons is below 140 mm. on the average, if they are acceptable for life insurance.

"General medicine, on the other hand, sees those who feel that they are sick. If their illness is due to abnormal blood pressure, it is usually high, frequently as high as 200 mm. or more. General medicine knows that these high pressures will come down to 170 mm. or 180 mm. by appropriate treatment, and many of the patients will live for years. But medicine does not realize that a small increase in the number of deaths each year means a

great difference to life insurance. At age fifty, we expect only 14 to die in the following year out of 1000 living, and we call that 100 per cent mortality. If 28 die, our mortality jumps to 200 per cent. At age sixty, if the number of deaths among 1000 living increases from 26.69 to 40.04, the mortality increases to 150 per cent.

"If a practitioner should see 1000 patients with high blood pressure at age sixty, and wager with himself that 974 would survive the year, and only 960 did survive, he would not feel downcast. In fact, he would probably point to the record with pride and boast of his ability in prognosis.

TABLE 6

The increased mortality associated with hypertension: (a) Fisher (156); (b) Rogers and Hunter (420); (c) May (316)

	MILLIMETERS OVER AVERAGE SYSTOLIC BLOOD PRESSURE FOR AGE	MORTALITY	EXTRA MORTALITY
		per cent	*per cent*
(a)	10–14	136.1	36.1
	15–24	183.8	83.8
	25–34	204.4	104.4
	35–49	248.5	148.5
	50 plus	414.7	314.7
(b)	10–25	146.0	46.0
	26–35	188.0	88.0
	36–50	248.0	148.0
(c)	Under 140	102.8	2.8
	141–170	133.6	33.6
	171–200	219.6	119.6
	200 plus	827.5	727.5

But life insurance would have to tell him that his mortality was 150 per cent in that group, and a medical director who did not make a better guess than than would not hold his job long. General medicine would look complacently at the living, but life insurance would ruefully regard the dead. . . . ."

The correlation between increased systolic pressure and heightened mortality has been demonstrated in the tables of Fisher (156), Rogers and Hunter (42), and May (316). Frost (167) has translated the extra mortality shown by Fisher into the actual number of deaths per 1000 persons with hypertension. In the case of a man, aged forty years, for example, it is shown that the single defect of a systolic blood pressure of 180 mm. decreases

his expectancy of life to that of a man of sixty-five years. His expected length of life would be further decreased, of course, by the occurrence of albuminuria (122), obesity (420) and other signs of physical impairment.

While the effect of diastolic pressure on longevity has not yet been established by large statistical evidence, in the two series of patients reported by Piersol (402) and Hamman (187), the mortality associated with a diastolic level of 110 mm. or over coincided closely with that following systolic hypertension of 200 mm. or more. Of Hamman's patients, one-third were dead in two years, two-thirds in six years, in each group; in ten years, 100 per cent of those with diastolic hypertension of this degree were dead, 98 per cent of those with systolic hypertension. Death within three years was the usual fate of Piersol's patients with systolic pressures over 220 mm., although one person carried for eleven years a pressure varying from 250 to 300 mm. It is remarkable how active and free from symptoms many of these patients may be: they operate machines in factories, drive automobiles and trucks, play golf, travel, occupy positions of responsibility, often undivided. To venture a prognosis requires accurate study and experienced judgment.

Along with the extra mortality brought out by hypertension, there must also be considered the causes of death. "The first circumstance" with which Bright (85) was impressed was the "extent and frequency to which the derangement of one organ (kidney) is connected with the derangement of others." Mahomed (303) analyzed 100 cases of "red granular kidney" in 1879 and noted that "by far the larger proportion of deaths from chronic Bright's disease is not from failure of the kidneys." There was heart failure in 17 cases, in 13 of which it was noted that valvular disease was lacking; cerebral hemorrhage in 15 patients; diseases of the lungs in 18; various medical diseases in 11 and surgical diseases in 13; and the "ordinary symptoms of Bright's disease" in 26. In recent years, essentially the same observations have been reported by Harpuder (188), Volhard and Fahr (482), Ehrström (129), Benni (60), Bell and Clawson (57), Hamman (187), and others.

Heart failure, usually of the congestive type, though the anginal type is also frequent, is the predominating cause of death. Cerebral hemorrhage and encephalomalacia are in second place and far exceed renal failure and uremia in the mortality data. While Bowers (80) gives uremia, with 36 per cent, first place as the cause of death in his series, if myocardial failure and coronary sclerosis are combined, heart disease occurred in 43 per cent.

Bell and Clawson, in 420 cases, found that myocardial failure had occurred in 187 and coronary artery disease in 67 more. Cerebral death occurred in

81, apoplexy twice as frequently as softening of the brain, and in direct proportion to height of blood pressure. Of the 36 patients (8.6 per cent) who died of renal failure, 1 had acute hypertension and uremia, 8 chronic hypertension and uremia, 8 chronic hypertension and acute uremia and 27 chronic hypertension and chronic uremia.

Ehrström noted in hypertensive patients that the appearance of symptoms commonly took place at about fifty years. A latent period preceded and an active period followed, each of about ten years. Thus the usual course of hypertension was run in twenty years, though frequently enough prolonged to thirty and forty years. In spite of a blood pressure of 200 mm., he found that a considerable number of patients were otherwise healthy and capable of work for ten to fifteen years. Therefore, he advises against

TABLE 7

Extra mortality, actual number of deaths and decreased longevity associated with hypertension at age of forty (after Fisher (156) and Frost (167))

MILLIMETERS OVER AVERAGE SYSTOLIC BLOOD PRESSURE FOR AGE	EXTRA MORTALITY	AVERAGE NUMBER DEATHS PER 1000; AGE FORTY	ACTUAL NUMBER DEATHS PER 1000; AGE FORTY	DECREASED LONGEVITY; APPROXIMATE YEARS
	per cent			
10–14	36.1	9.79	13.32	10
15–24	83.8	9.79	17.96	14
25–34	104.4	9.79	20.01	17
35–49	148.5	9.79	24.04	19
50 plus	314.7	9.79	40.59	25

a pessimistic attitude in the prognosis of hypertension. Weiss (491) also noted that many patients had a favorable arrest or even regression of their high pressure. Benni states that the majority of his patients lived to at least fifty-five years and a great part of them attained the age of seventy years. Within four years of first coming for treatment, however, the greater part had succumbed.

In Aschoff's clinic Rosenthal (428) studied the ages and causes of death according to the type of kidney disease. He found that 16 per cent of the patients with benign nephrosclerosis died of uremia, compared with 5 out of 7 with malignant nephrosclerosis. This clinico-pathologic distinction he could not make. Two malign cases lived more than ten years.

At the Mayo clinic, Keith (241) found that the average length of life after the diagnosis of malignant hypertension had been made was eight months. Of 81 patients, 73 (90 per cent) died within fifty-one months, and

the majority within two years. Only 5 lived two years or longer. The malignant process is frequently engrafted upon the benign form: in one of Keith's patients, and in a woman whom I studied, there had been hypertension for four years. Blood pressures in this group are extraordinarily high, diastolic hypertension of 200 mm. being recorded by Keith. The ages lay between thirty-five and fifty years. Klemperer and Otani (254) noted that 72 per cent of their patients were under fifty years, the reverse of the "benign" form.

From the date of the first discovery of high blood pressure, Hamman found that 10 per cent of his patients were dead in two years, 30 per cent in 5 years, 78 per cent in ten years. From the date of his examination, 90 per cent were dead in ten years. In the examination of these patients, the facts

TABLE 8

Prognosis in renal disease, Rosenthal (428)

	SECONDARY CONTRACTED KIDNEY	PRIMARY CONTRACTED KIDNEY		ARTERIOSCLEROTIC KIDNEY
		Benign	Malignant	
Age at death	30–40	40–70	20–50	70–80
	per cent	*per cent*	*per cent*	*per cent*
Apoplexy	5.26	20.0	14.0	15.0
Heart	26.32	32.0	14.0	35.0
Uremia	42.11	16.0	72.0	0
Intercurrent diseases	26.00	32.0	0	50.0

which he found of unfavorable import were (1) a blood pressure of 200/110 or over; (2) cardiac enlargement; (3) the presence of albumin and casts in the urine; (4) diminished renal function, as measured by phenosulphonephthalein output and fixation of specific gravity; (5) changes in the retinae. Ellis and Marrack (132) and Benni (60), among others, have made similar observations concerning retinitis and diminished renal function. When moderate and severe retinal lesions were to be seen, the ratio of deaths in the first two years was more than fourfold the number of deaths in patients with slight or no fundus changes, and 3 to 1 in the first five years (Hamman). Of 9 patients with an average age of thirty-three years, and an average systolic pressure of 220, all were dead within four months. Of 10 patients averaging forty-nine years, and a systolic pressure of 245 mm., five were dead in six months (Ellis and Marrack).

The prognostic importance of the lack of normal cardiac response is

emphasized by Herrick of New York (200). The cardio-respiratory test of Frost has given its author "information otherwise unobtainable" in evaluating cardio-vascular disease (167).

Electrocardiographic evidence of heart muscle disease has been summarized by Horine (211). When the T-wave was inverted in all leads, together with an upward S-T convexity, no patient lived longer than a year, and the majority only a few months. The "coronary T-wave" in the first two leads, or in the third lead with an inverted T-wave in lead II, was followed by death within two years.

Bundle branch block is another ominous sign. In Horine's cases, it preceded death by eighteen months or less. Willius (500) found hypertension present in 52 per cent of his 105 patients with complete bundle branch block and the average length of life in the whole group was fourteen months.

TABLE 9

Causes of death in patients with hypertension

NAME	NUMBER OF CASES	HEART	CEREBRAL	RENAL	OTHER
		per cent	*per cent*	*per cent*	*per cent*
Janeway	176	43.0	38.4	26.0	
Volhard and Fahr	125	82.0	18.0	0	
Ehrström	46	30.4	30.4	26.0	13.0
Fisher	507	29.6	21.1	20.9	28.4
Harpuder	165	53.9	38.4	7.7	
Benni	142	47.1	39.5	2.1	11.2
Bell and Clawson	420	60.0	19.5	8.6	11.0
Hamman	96	30.0	27.0	19.0	24.0

In spite of exceptions, it must be said in summary that the prognostic data indicate that hypertension as the cause of progressive vascular disease shortens life materially according to its degree of severity. The picture as a whole is depressing. But it is brightened by the experience with the favorable course of hypertension in individual patients. In the Bright oration, in 1927, W. S. Thayer recounted a prognostic downfall, of the happier sort, in the case of the man who is rated among the five or six medical geniuses. A physician of forty-five years went to Richard Bright because of marked albuminuria, and received the opinion that he had less than two years to live. He gave up practice, retired to a quiet life in the country, lived comfortably for forty-three years, the albumin in the urine persisting, and died of cerebral hemorrhage at the age of eighty-eight.

Such examples of the benefits of a change in environment or of habits have come to the attention of all of us. They bring the thought of what can be done to increase the length and content of life when enlightened public opinion and social and economic support shall give full scope to preventive medicine.

In the face of the undeniable and disconcerting effects of persistent hypertension on health and longevity, the words of Stephen Paget, in his "Confessio Medici," are worth recalling: "If medicine is an art, what works of art does the doctor produce? None says Claude Bernard, le médecin artiste ne crée rien; but surely he is wrong. The doctor, so far from creating nothing, creates life; for he who saves or prolongs life, creates more life."

TABLE 10

The chief causes of death in the United States

Rate per 100,000 population in the Registration Area. From Statistical Abstracts, Bureau of the Census 51:82, 1929

	1928	1927	1926	1920
Heart diseases	207.7	195.7	199.1	159.3
Cancer	95.9	95.6	94.9	83.4
Nephritis, acute and chronic	95.0	92.5	98.3	89.4
Apoplexy	91.3	87.3	89.0	86.4
Tuberculosis	79.2	80.8	87.1	114.2
Pulmonary tuberculosis	71.4	72.5	77.8	100.8
Influenza and pneumonia	103.7	69.4	99.3	153.7
Bronchitis and broncho-pneumonia	44.7	39.2	50.5	67.9
Diabetes mellitus	19.0	17.5	18.0	16.1
All deaths (per 1000)	12.04	11.4	12.2	13.1

Upon the patient, also, much depends for the conservation of his vascular reserve. For those who will heed the words of wisdom, no better advice can be given, no saner attitude toward life, than is contained in Allbutt's discussion (9a) of aortic disease:

"If the patient, whether in a palace or in a workhouse, be a man of easy circumstances and tranquil occupations, he has the greater chance of survival. Care or worry, bustle or toil, will kill him. There are men of such a temperament that they cannot form sedate habits: recklessly, as it seems to the doctor, they skip up stairs two at a time; they puff after trains; they climb over five-barred gates; they bounce up from deep sleep to pass water, and so forth; they do not mean to run these risks, but such is their incorrigible temperament. With such persons discipline must be attained

by spending day after day in drill, in gaining self control, in repressing volatility. In this precaution, there is nothing false to a man's best self: it is the way to get the most work out of himself before he dies. Persons in toilsome callings must change them; and spend the perhaps no less useful remnant of their days in some easier duties. Due vigilance may be exercised without the encouragement of hypochondria; as some one well put the rule: find out what you can do and do it; find out what you cannot do and never do it."

CHAPTER X

Treatment

I. General Measures

The crux of the problem of hypertension, from all the accumulated evidence, lies in the increased activity and tone of the smooth muscle cell of the arteriole.

Of this functional nature, acute paroxysmal hypertension is the clearest proof. The underlying pathophysiologic state of the small vessels is visible and unmistakable; the symptoms and signs indicate widespread and severe vascular spasm; and when stimulation ceases, the vasoconstriction subsides and vessels and blood pressure and patient return to a normal state.

Precisely the same disturbances in vascular function are found in persistent hypertension, however mild, except in respect to tempo. Beyond this, the duration and degree of the hypertonus inevitably add the element of structural disease in the small and smallest vessels.

Between these extremes of acute and chronic hypertension there occur all possible gradations in rate of development and severity of process—eclampsia, nephritis, malignant hypertension illustrate this transition. Changes in the contractile tissue of the peripheral stream bed are common to all.

The control of this state of abnormal tonus and contraction must be the aim of all measures for the prevention and relief of hypertension. Handicapped by lack of the fundamental knowledge of cellular physiology which must be acquired before precise methods of treatment can be applied, our present resources of prevention and therapy can be directed toward these objectives:

1. The sources of vasomotor instability and stimulation.
2. The means by which these stimuli are mediated.
3. The mechanisms by which they are carried into effect.

To control the sources of stimulation, and the soil on which the stimuli fall, is to be able, our knowledge of the nature of hypertension already reveals, not only to remove a suprarenal tumor, or a focus of infection, or to regulate a disorder of metabolism, but to determine heredity, influence environment, education, development, and manner of living. Eugenics,

as an attempt to correct the unwise choices of ancestors, and get our patients, at least of the future, well born (49); psychology wisely applied in home and school during the formative years of childhood in order to avoid the complexes that may so greatly mar later life (186); even philosophy, to take a hand in the remaking of human nature (205) and persuade toward the pursuit of forgotten "highest goods"—these are assuredly a part of the foundation problems of a disease so deeply rooted in psyche and soma as hypertension. By no means should these matters be foreign to the interest and thought of the discerning physician and wise counsellor.

To influence the centers which receive the stimuli and the pathways which transmit them to the vessels, is the second means of approach. Largely the sympathetic nervous system is here concerned. Regulation of the vasomotor center is so dominated by mental and emotional elements as well as by the physical factors of quantity and quality of blood supply that there is wide opportunity for therapeutic modification. Section of the nerves in their course (282, 430) is one purely mechanical means of removing the stimuli they carry to the field of action in the arterioles. Another means, the alteration of the response of the neuromuscular junction—by the use, for example, of calcium or parathyroid or atropine (27) (261)— has possibilities which are by no means well understood.

The restoration of the normal activity of the arteriolar smooth muscle cell is the third possibility in the treatment of hypertension. A working knowledge of the alterations in the physico-chemical activity of the cell is the physiologist's goal, toward which a start has been made, but with facts and inferences obviously still obscured by faulty and incomplete data. Meanwhile, the attempt to remove the "metabolic load" by restriction of the diet as a whole or of its particular constituents must remain an important working method of the clinician in dealing practically with the sick man.

The present status of the treatment of hypertension, in spite of the various general and special methods of approach to be discussed, has many analogies to the treatment of diabetes mellitus in the era before insulin. By semi-starvation, restriction of activities, and an attempt at a "transvaluation of values" in the patient's world, he can be relieved of a great deal of strain and the blood pressure often be reduced. But the results thus obtained are likely often to be as pathetic as were those in the undernutrition treatment of severe diabetes. In the care of those who suffer from hypertension and its complications—the failing heart, the threat or the fall of the apoplectic ictus, the blindness of retinal disease, all the ills of body and mind to which the relentlessly advancing vascular lesions lead—the physician learns full

appreciation of his limitations, and yet opportunities "sometimes to cure, often to relieve, always to console."

Perhaps, however, it is not idle to think that the equivalent of insulin might be discovered for hypertension. MacWilliam (300) has advised "an open mind as to the possibility of a solution being found in an unexpected direction." Depressor substances are already sufficiently effective to keep discussion alive concerning the advisability of their use.

After all, no argument concerning the reduction of high blood pressure by therapeutic means can alter two main facts. One is the amply sufficient clinical evidence that the fall in arterial tension, when the latter is uncomplicated by advanced vascular disease, and the reduction is not brought about by cardiac weakness, is often immediately followed by the remission of symptoms and the patient's sense of well being. The second fact, supported by all we now know of its evolution, is that if hypertension can be controlled early in its course, it will not, by its persistent and progressing vascular strain, give rise to the damaging sequelae. Disturbance of function is far more amenable to treatment than alteration of structure.

To illustrate the concrete problems of management which hypertension presents, the following record is cited:

T. N. O., a white man, aged twenty-five years, a bond salesman, has had no symptoms of ill health, but in June, 1927, at an examination for life insurance, his systolic pressure was found to be 196 mm. He had just graduated from college, where he had indulged strenuously in baseball, hockey and golf without any evidence of disability. After extreme exertion, there was palpitation, but no dyspnea had ever been noted.

The patient's father, at fifty-six years, has a systolic pressure varying from 160 to 170 mm. The mother died at fifty-two, of hepatic carcinoma, six months after a tumor was found in the breast. A paternal grandparent and aunt died of Bright's disease. There are no other children. The patient resembles his father.

Chicken pox, measles and mumps in childhood and pneumonia without complications, at seventeen, is the record of past illnesses.

Following the discovery of the high pressure, the patient submitted to thorough study, with no pathological findings. Until 1927, he had been a free user of salt; now he discontinued its use and ate a minimum of "red" meat. He has a steak "once in six weeks." On this diet during the year following, his blood pressure was found at several examinations in the neighborhood of 190 mm.

He has no headaches, sleeps nine hours, has regular bowels, and no nocturia.

Physical examination (January, 1929) revealed a well developed, stocky, shortnecked young man, of blond complexion, not plethoric. His height is 70 inches, weight 158 pounds. The head is rather broad, the eyes set at a medium distance apart. There is no acrocyanosis. The demeanor is calm, but there is appreciable perturbation at being examined.

The eyegrounds show no vascular change. The heart is not enlarged. The blood pressure is 170/80, rate 84. The urine is free from albumin and caste.

Reëxamination in November, 1929, reveals a blood pressure of 172/90, rate 84. The brachial arteries are moderately tense, but not definitely thickened. On percussion and fluoroscopy, heart and aorta show no changes. The urine is clear.

With the appearance of perfect health the patient in one part of the examination disclosed the lack of adequate vasomotor control. In a standard test (Schneider (444)) for circulatory efficiency, his score is 8 instead of the perfect 18. Resting recumbent, his pulse did not fall below 84 per minute, rose to 102 on standing, and showed a further rise to 108 on exercise. His blood pressure rose only 2 mm. on standing.

He sleeps well, eats meat once daily, uses no extra salt, and smokes a dozen cigarettes. He perspires freely, perhaps excessively. His hands are always warm. He believes his reaction to excitement is greater than formerly. Having become engaged, he now wishes to be told the advisability of getting married.

Here, then, in the person of an exceptionally intelligent and coöperative young man, is the problem of pure hypertension uncomplicated by cardiac and vascular changes. He lives in a rational way, without devoting too much thought to his physical condition; yet his heredity suggests the inborn nature of the disease, and the height already attained by his pressure can hardly fail to influence decisively his own longevity. He comes for advice and what has the physician to offer?

Apart from the fact that it would be useless to advise the patient not to marry, I am not certain that marriage will not have a favorable influence. It is likely to provide a steadier and quieter life, and a background of greater repose and satisfaction than would be true otherwise. Inquiry discloses that his future wife understands the situation and has had training which will permit her to be an earner if the necessity arises. As a pure experiment in the transmission of a Mendelian character, the biologist might object to the mating, but until natural selection is overruled by eugenic choice, the level of blood pressure is not likely to play a recognized rôle in romance. Moreover, it is not certain that hypertension will continue

as a dominant unit or that other qualities to be transmitted do not warrant the risk run from this one character by the succeeding generation.

It suffices to say that these compromises between the claims of life, and penalties imposed by the disease, are not always easily chosen or attained. Medical men of my own acquaintance, who knew all the chances, have preferred to die in harness, in the full tide of life; but, by way of contrast, others have given up necessarily harassing practice to become in one case an editor, in another a breeder of fine cattle—changes of occupations which are much more satisfactory to themselves and to many other people, than the cerebral hemorrhage or coronary thrombosis of their colleagues.

The management of hypertension, in perspective, requires a consideration of the patient as a whole, his constitution, personality and background of heredity and environment. Its details must include possible adjustments in his manner or living, with particular attention to work, recreation and rest; the correction of dietary habits, especially in regard to the excessive use of salt, carbohydrate and protein, and often the insufficient use of water; weight reduction in the obese; the removal of foci of infection and the symptomatic use of sedatives, of ovarian and thyroid gland, of digitalis and vasodilators, of the saline purgatives, and of many other useful agents and measures, even including surgical operations, which special conditions suggest. In the easily available recent American literature, the presentations of Foster, Paullin, McLester, O'Hare, Mosenthal and Moschcowitz, among others, cover the general treatment of hypertension in its various phases.

In early hypertension, before the diastolic phase of the blood pressure becomes elevated, and restitution to normal is still possible, the simple regulation of diet and exercise, Foster states (161), is often sufficient to produce surprising results in improving the patient's general health and correcting the metabolic disorder on which the high blood pressure rests. For others, a new environment and a system of reëducation is necessary. "No result worth securing can be attained in a short period of time."

As a general rule, Foster believes that the treatment of hypertension cannot be carried out at home. The patient's mode of life and first of all his mental attitude toward his surroundings must be made over. For the patient with early hypertension sanitoriums are the ideal, conducted along the lines of a summer camp, with the "sports atmosphere" and exercise in the form of games, which at once "fix mental attention, harden flabby muscles, consume calories and reduce weight, and correct the person's philosophy of life." If secondary myocardial or vascular complications have arisen, rest and observation must precede this régime of exercise.

"The chief obstacles to treatment are first that the patient with hypertension feels perfectly well at the stage when treatment is most likely to succeed, and second, that economic obstacles stand in the way of such treatment over a period of months. . . . . It is not so much that the disease cannot be remedied as that the remedy is not attainable for many." For the majority, the best plan of treatment must be regulation of activity and compromises in diet.

The beneficial effects of moderate exercise in comparison with a rest cure are often impressive. A woman physician, aged fifty years, consulted me because of moderately high pressure. At the last of a number of clinics she had visited she was advised to go home and stay in bed. Her blood pressure, which had not prevented her from getting insurance at forty-five, was 150 at forty-six, 210/110 at forty-eight, and since had reached 230/130, coincident with the complete cessation of menstruation. Rest in bed had only a transient effect on the pressure, and was decidedly boring to this woman of active habits. Deciding to give up the bed and resume social activities, she discovered that after the relaxation of dancing, her pressure fell to 150, lower than during the period of complete physical inactivity.

The value of physical exercise within the limits of tolerance is now happily accepted for many of the forms of chronic circulatory disease and often has made useful people out of those who easily might have been doomed to a neurotic invalidism.

McLester (320) puts regulation of the manner of living first in the treatment of hypertension and advises three to four weeks in bed under conditions of complete relaxation. Diet is important, but not predominant. Foci of infection are to be removed. Venesection is advised when uremia is impending.

Rolleston (422) has summed up his general viewpoint in the following: "A hard-working and hard-living man of affairs must relax and reduce the stress and strain of his existence; he must learn to play, to take real holidays and frequent days and week ends off, to follow hobbies and avoid overeating. . . . . Regular exercise within his powers should be encouraged. The moral is moderation in all things. . . . . "

Not far different from the American and English attitude is Munk's (353) attempt to study the patient in his relation to his particular susceptibilities and weaknesses, to regulate purposefully his manner of life, and to spare the heart by suitable dietary restriction. For the higher levels of hypertension he recommends rest in bed, both for the relief of symptoms and for the opportunity it affords of studying the patient and pointing out the proper lines of future conduct. Vaquez (477) offers essentially the same hygienic advice.

It is only fair to say that there is a minority which is not impressed with the importance of psychic and physical stress, heredity and environment. F. M. Allen (13) has stated that "the great majority of cases of hypertension, whether simple or complicated with other conditions, are more or less completely relieved by the single measure of salt-free diet, carried out thoroughly and accurately over a sufficient length of time. The results are not due to chance, psychic influence, rest, reduction in weight, or other imagined agencies." His view is that infectious or toxic damage renders kidneys and vessels susceptible to functional overstrain through the chemical agency of diet, and that civilization, with its sedentary life, long hours, and psychic stress and strain, is not known to cause either heart or kidney disease, though a popular idea makes them responsible for blood pressure. Neither physical nor mental exertion cause high blood pressure, which is "not a monopoly of financial magnates nor a flattering indication of great brain power and responsibility." Unfortunately for simplicity in treatment, as well as for a solution of the nature of hypertension, the results of Allen have not found corroboration.

Diet

Much of the empiricism in diet for hypertension, as for other diseases, has vanished with the clinical application of the newer knowledge of nutrition, and the opportunities for precise control by means of blood chemistry and the study of total metabolism. The reaction against the absurdities committed in the name of dietotherapy is expressed in Horder's (210) words that "not upon how meagre a diet a patient can live, but on what sort of a diet he can live most efficiently, should be the physician's guiding principle in ordering a patient's regimen." Such a diet will meet the requirements of: (1) energy; (2) nitrogen balance; (3) proper ratio of carbohydrate to fat; (4) vitamines; (5) inorganic salts, and (6) fluid. According to Sansum, (368) it must also bring about an alkaline reaction of the urine by reason of a preponderance of alkaline ash foods. Straub (464) also emphasizes this acid-base balance in the diet. In hypertension, it is almost always necessary to deal with some or all of these factors.

Reduction in weight by means of a sub-calory diet is often the first practical way of helping the patient rid himself not only of the mechanical burdens which obesity throws upon the circulation, both by its load and by embarrassing heart action, but also of a less evident interference with tissue oxidation, and normal cellular activity. The beneficial effects of weight loss on symptoms, blood pressure, circulatory insufficiency, and cardiac signs have been reported by a large number of observers (54, 161, 314, 469).

From the patient's standpoint, it is not unimportant that the diet be palatable and satisfying.

In the absence of nitrogen retention, the hypertensive patient is no longer subjected to unnecessary restriction of protein. From 60 to 75 or even 100 grams of protein per day—approximately 1 gram per kilogram of body

TABLE 11

Corrective diet high in protective foods (Langstroth)

FOOD ITEMS	CALORIES IN PROTECTIVE FOODS	CALORIES IN NONPROTECTIVE FOODS
Breakfast:		
Glass of orange juice	100	
Two eggs	166	
Fresh fruit	80	
Glass of milk	160	
Lunch:		
One-third head of lettuce	16	
One tablespoonful of oil		93
Two fresh vegetables	80	
One pat of butter		95
Two glasses of milk	332	
Fresh fruit	80	
Dinner:		
Meat		190
One-third head of lettuce	16	
One tablespoonful of oil		93
Two fresh vegetables	80	
One glass of milk	160	
Fresh fruit	80	
Cheese		91
Handful of nuts	140	
Totals	1490	657

Total calories, 2147. Percentage of protective foods, 70. Carbohydrates, 175 grams. Protein, 80 grams. Fat, 110 grams.

weight is permissible, and only retention of nitrogen is an indication for restriction of protein to the level which will maintain a normal blood urea value. Especially in the presence of albuminuria, Peters (399) has shown the importance of preventing nitrogen wastage by an adequate intake of protein. The traditional distinction between red and white meat has gone

into the discard, though the extractives of meat are generally frowned upon, and the disadvantages of meat among other common foods as the precursor of an acid ash has been stressed by the California citrus fruit school. Joslin (233) has written recently of the possible rôle of eggs—from their cholesterol content, however, rather than protein—in the production of vascular disease. Liver would come under a similar suspicion.

In spite of the growing tendency to a greater use of fruits and vegetables, concern regarding the disproportionate amount of carbohydrate in the American dietary is borne out by Langstroth's (269) analysis of the diets of 501 patients. Bread and butter appeared in the diets of all but 6 of this series, meat in all but 31, potato in all but 107 and sweet desserts in all but 128. There was a dearth of the protective foods—eggs, milk, fruit, and lettuce. These amounted to only 12 per cent of the average diet. The incidence of degenerative disease, hypertension being here included, Langstroth points out, increases as the percentage of protective food goes down. The clinical picture of premature deterioration of all the body tissues—bluish gray sclerae; tongue dull bluish or grayish pink and often furred; skin sallow, coarse and thick, in middle life with multitudes of dilated venules over cheeks, nose and ears; protruding abdomen and overweight—suggests to him that food as well as constitution must be considered as an important etiological factor in high blood pressure and other chronic diseases. His patients were often greatly benefitted, indeed apparently revitalized, by a diet containing 70 per cent of protective food and 2100 calories, considerable loss of weight frequently resulting.

Reduction in weight, even at the safe rate of 1 or 2 pounds per week, often requires a diet restricted to 1500 calories per day, and often much less, as Grafe (176) showed in the case of constitutional obesity. Protein in these patients is kept at a safe level and the diet is lowered at the expense of fat and carbohydrate. The diabetic dietary, with a smaller quota of fat, can be transferred easily to the treatment of the obese hypertensive.

In loss of weight, another factor which is of importance is the release of tissue fluids—"invisible edema"—which follows the use of a salt-poor diet.

It has been noted that O'Hare and Walker (373), Mosenthal (344, 345), McLester (320), and most recently Berger and Fineberg (62) were unable to reproduce the results reported by Allen and his co-workers with the salt-free regimen in hypertension. Allen (15) maintains, however, that "nobody has experience upon which to base criticisms unless he can prove that the sodium chloride in the daily urine has been kept below 0.5 grams during a sufficient period of time." This time limit may be several weeks because of prolonged retention of salt in the tissues. In successfully treated

cases, Allen claims that the progressiveness of hypertension is halted, and barring violations of diet, infections and accidental complications, "a

TABLE 12

A salt-free reducing diet (Allen); Calories, 776

FOOD IN GRAMS	NaCl	PROTEIN	FAT	C.H.
Breakfast:				
Grapefruit, 100	0.0045			5.0
Toast, 20	0.0252	2.0	.2	11.0
Egg (1)	0.0900	7.0	5.5	
Cream (for coffee), 20	0.0272	.6	4.0	1.0
Butter (salt-free), 6	0.0078		5.1	
Lunch:				
Chicken, lean, 80	0.0904	14.4	9.6	
Cranberry sauce, with saccharin	0.0075			5.0
Fresh asparagus, 100	0.0066	2.0		3.0
Lettuce, 50	0.0625	.5		1.5
Tomato, 50	0.0285	.5		2.0
Cucumber, 30	0.0171	.3		.9
Mineral oil mayonnaise				
Strawberries, 80	0.0080	0.8		5.6
Bran wafers				
Dinner:				
Steak, 90	0.1348	21.0	9.0	
Mushrooms, fried in mineral oil, 100	0.0360			
Spinach, 150	0.1875	3.0		4.5
Lettuce, 50	0.0625	0.5		1.5
Grapefruit, 50	0.0022			2.5
Orange, 40	0.0040	0.4		4.0
Custard with saccharin	0.0900	7.0	5.5	
Total	0.8928	60.0	38.9	46.5

For a great variety of salt-free diets, at all caloric levels, reference is made to Allen's "Practical Manual" (Part I, Treatment of Kidney Diseases and High Blood Pressure), Morristown, 1925. For obesity reducing diets, the author has used with much satisfaction the food tables and equivalents in Huddleson's "Food for the Diabetic," Macmillan, New York, 1923. The Adult Weight Conference's volume, "Your Weight and How to Control It," Doran, New York, 1927, is of value to the patient.

good result once obtained is permanent." . . . . "For this reason any advice that hypertension should be ignored, or should be treated with rest or other palliatives is pernicious."

Mosenthal states that the lack of prolonged control periods rob the studies of Allen and Sherrill and of Vogel of much of their value.

In an experience with 328 patients, mostly with severe hypertension, over a six-year period, Allen (15) reports a total mortality of 43, or 13.1 per cent. "Admitting the record of approximately 110 failures among 328 cases, based on the objective fact that there was no important reduction of blood pressure, the total of 43 deaths in six years would not make a very bad percentage if based on the failures alone, without regard to the rest of the series. Our actual belief is that the salt-free diet is beneficial in practically all cases, and that it has at least mitigated symptoms and prolonged life even in the majority of cases classified as failures."

The salt-free diet, Allen states, means that no salt is to be added either at the table or in cooking, that all kinds of smoked or preserved meat and fish and canned soups are to be avoided, that no cheese except cottage cheese is acceptable, that baker's bread and other bakery products are prohibited. Prepared cereals, canned fruits and vegetables, syrup and molasses have an unsuspected salt content. Most nuts and a few fruits, such as bananas, and milk are sufficiently rich in salt that moderation in their use is required. Shell fish are limited to those procured in fresh water, and vegetables if used in large amount may require thrice boiling.

Thus it is evident that the diet is somewhat expensive and hard to follow, especially at home, while the food quickly may become unpalatable. The hypotensive effect of the salt-free diet has been ascribed by its opponents to a loss of appetite, undernutrition and general weakness. Sodium malate recently has been proposed as a substitute for table salt.

It is difficult to leave the unsettled subject of the relation of sodium chloride to hypertension without expressing the feeling that Allen's view of the problem, though narrow, supports the conception of altered mechanisms in the smooth muscle cell, which by withdrawal of one electrolyte, give place to new physico-chemical processes. It is, of course, a negative manner of approach. The substitution of other anions and cations for sodium and chlorine is one of the attractive possibilities of the use of specific agents (505).

In addition to the normal requirements of the body in respect to fluid intake, evidence has been brought of the washing out of metabolites in the diuresis following ingestion of water up to several liters. This is the main advantage attributed to the "Trinkkur" at spas and mineral springs, though the mineral waters have alterative and purgative effects and the relaxation and rest in the environment of a resort is an important adjuvant in lowering high pressure. Miller and Williams (327) found that larger quantities of water—10 liters per day—caused a rise in blood pressure. Sir

James MacKenzie, among others, has given his experiences and a candid estimate of the Nauheim treatment in heart disease which is equally applicable to the spa treatment of hypertension. "So remarkable are these waters that it is claimed that they can increase the pressure when it is low, and lower the pressure when it is high."

The reduction of high blood pressure by means of specific therapeutic agents has been and is looked upon by many as of doubtful value. Morawitz (333) notes that some patients feel worse during the period of lowered pressure, and has observed a rise in venous pressure and an increase in the size of the spleen as signs of stasis. Volhard (483) recently said that he has dispensed with drugs in the treatment of uncomplicated hypertension and relies on dry diet and salt deprivation to diminish blood mass and thus blood pressure. Rappaport (410) has cited the literature and given his own results in the therapeutic endeavor by means of deep breathing to increase the blood mass in the pulmonary circulation in favor of its decrease in the aortic system. O'Hare (377) writes that drugs aimed directly at the reduction of blood pressure are of little value. It has been said that a fall in pressure pleases the doctor but rarely helps the patient. Miller in Chicago has stated that his advice to patients, outside of reducing weight and strenuous exercise, is to cultivate calmness.

If hypertension were to be regarded as a purely compensatory process, the point of view that its reduction is unphysiological would be justified. It is undeniable that hypertension of long standing has produced irreversible structural changes in the cerebral or coronary arteries which will not permit the blood pressure to be reduced without seriously upsetting circulatory equilibrium and the patient's well being. The clinician must choose patient and therapy with judgment. In my own hospital practice, with patients who represent as a rule the end stages of hypertensive vascular disease, I do not attempt any sharp reduction of the blood pressure. Rest and diet, in the first place, are factors which for the first week or two of the stay in hospital are likely to obscure the effect of any drug which might be used, and by that time, the patient is usually disinclined or unable to remain for longer observation. As a matter of fact, it has been my experience that significant and lasting reduction in severe chronic hypertension is frequently impossible, either by diet, drugs, venesection or withdrawal of cerebrospinal fluid. In this group of patients, who perhaps make up 20 per cent of the whole, I have regarded the absence of a fall in tension as evidence of an active compensation, which nature takes care not to have broken. For a period of six months, I had the opportunity of observing a man with recent hemiplegia whose hypertension remained throughout the period with little

variation at a level of 220/110, with a pulse rate of 100 to 120. A month of salt-free diet, repeated venesections, a series of lumbar punctures which revealed cerebrospinal fluid under increased pressure (20 to 40 mm. Hg) and relieved papilledema and Cheyne-Stokes breathing, and large doses of vasodilators, all had no effect on the level of blood pressure. I am convinced that the lowering of the pressure of such a patient, if it were possible, would

TABLE 13

Acid and alkali forming foods (from Sansum's "The Normal Diet," after Sherman and Gettler)

ACID ASH	N/1 PER 100 GRAMS	ALKALINE ASH	N/1 PER 100 GRAMS
	cc.		*cc.*
Bread, white	7.1	Almonds	12.38
Bread, whole wheat	7.3	Apples	3.76
Corn, sweet dried	5.95	Asparagus	.81
Crackers	7.81	Bananas	5.56
Eggs	11.10	Beans, dried	23.87
Egg white	5.24	Beans, lima, dried	41.56
Egg yolk	26.69	Beets	10.88
Fish, haddock	16.07	Cabbage	4.34
Fish, pike	11.81	Carrots	10.82
Beef, lean	13.91	Cauliflower	5.33
Chicken	17.01	Celery	7.78
Pork, lean	11.87	Chesnuts	7.42
Veal	13.52	Currants, dried	5.97
Oysters	30.00	Lemons	5.45
Oatmeal	12.93	Lettuce	7.37
Peanuts	3.9	Milk, cow's	2.37
Rice	8.1	Muskmelon	7.47
		Oranges	5.61
		Peaches	5.04
		Peas, dried	7.07
		Potatoes	7.19
		Radishes	2.87
		Raisins	23.68
		Turnips	2.68

be at the expense of immediate failure of cerebral or cardiac or renal function.

As evidence of the ill effect of progressive decrease of blood pressure, Dumas (124) has described the physical and mental weakness which follows the involution of hypertension in the aged. In his senile patients, the fall in pressure was not due either to cardiac weakness or to cachexia. He cites the case of one vigorous old person who ordinarily carried an arterial tension

of 220/150. During several successive winters, attacks of pneumonia were accompanied by a gradual fall of blood pressure to 150/80. At this level there was extreme asthenia, for a time bordering on coma, until by tonics and diet the blood pressure was restored to its former level and the patient recovered her strength and activity.

Examples of acute lowering of hypertension Batty Shaw (449) has described under the name of "hyperpiesic crises." These are marked by a sudden fall of blood pressure, with or without convulsions, collapse, and coma, which he states may possibly be due to the release of histamine-like bodies from the splitting of body protein following infection or stoppage of blood supply. The blood pressure quickly returns to normal and the attack is over. The same syndrome of acute hypotension, but without this quick return to the former level, occurs in coronary thrombosis with infarction of the wall of the left ventricle.

A striking example of weakness, loss of consciousness, transient hemiplegia, and Cheyne-Stokes breathing in a hypertensive patient whose systolic blood pressure fell to 170 mm. during a train-ride was reported by Fleming and Naffziger (157). The pressure rose in twenty-four hours following treatment—foot of the bed raised, fluids, brisk rubs, caffeine and strychnine—to 245 mm. with relief of symptoms.

Another striking example is the acute involvement of the vasomotor center causing loss of blood pressure, which is one of the chief dangers in spinal anesthesia (394) and is effectively treated by the prompt intravenous use of adrenalin. Fortunately it is easily guarded against by proper preparation and technique.

Karell diet for congestive heart failure or nephritic edema; New York Hospital

For first 5 to 7 days:
200 cc. milk at 8 a.m., 12 noon, 4 and 8 p.m.
No other fluids or food.
Eighth day:
Milk as above.
10 a.m.: 1 soft-boiled egg.
6 p.m.: 2 pieces of dry toast.
Ninth day:
Milk as above.
10 a.m.: 1 soft-boiled egg and 2 pieces of dry toast.
6 p.m.: 1 egg and 2 pieces of dry toast.
Tenth day:
Milk as above.
12 noon: Chopped meat, rice boiled in milk, vegetables.
6 p.m.: 1 soft-boiled egg.

No salt is used with diet, and a small amount of cracked ice may be allowed. Often with the rapid disappearance of edema, the milk diet may be modified, but limitation of fluid, protein and salt intake is continued with advantage.

II. SPECIFIC MEASURES

In the treatment of functional hypertension, and until the anatomic component decreases vascular reactivity to a point where arteriolar dilatation is impossible, or at best, a doubtful gain, drugs have a distinctly valuable place in supplementing general measures of hygiene.

"To warn a person against worry is easy," Rolleston says, "but such advice is more helpful when backed up by a prescription for a bromide mixture to insure some standard of philosophic calm."

The benefits of drugs, moreover, are not entirely psychological. It is clear that they may and do take an important part in altering the cellular activities which underlie hypertension. As knowledge of cell physiology expands, it is surely to be expected that control of other physico-chemical processes in the animal body will become as precise as that of insulin over the combustion of glucose.

Lowering of high blood pressure by drug therapy is brought about in three principal ways: (1) by regulation of the activity of the vasomotor center; (2) by decreasing arteriolar tone; and (3) by depression of heart action. Since there are few occasions when it is justified or advisable to seek directly to diminish the contractile force of the heart beat, the agents of choice in the treatment of hypertension are the sedatives and the vasodilators. A further possibility is the decrease of the blood mass or blood viscosity, by means of saline purgatives, but the weakening effect of this method, like that of venesection, forbids a too frequent repetition.

When high pressure is reduced by lowering of peripheral resistance, careful objective study (411, 496), as well as the absence of symptoms, has shown no diminution of renal function, as determined by the kidney's ability to dilute and concentrate urine, by excretion of urea and the absence of nitrogen retention in the blood. On the contrary, widening of the visible capillaries and improvement of circulation in the peripheral bed has been noted after a reduction in arterial pressure of 40 to 60 mm. Hg, so that normal metabolic exchange is accomplished with the conservation of cardiac and vascular energy.

In contrast with the doses of bromide and of iodide which are usually prescribed, the vasodilating effect of extremely small amounts of these salts has been reported by Guggenheimer and Fisher (181). Both by animal perfusion and by clinical trial, it was found that the optimal dilator effect was obtained at dilutions in the body of 1:5 million for the bromide and 1:4 million for the iodide. Since the normal concentration of iodide in human blood lies between 1:8 to 1:12 million, the amount of potassium iodide that is theoretically required to maintain this effective level of vasodilatation is

only 5 mgm. three times a day. Practically it was found that combination with the iodide of an equal amount of potassium bromide gave better relaxation. Their prescription was:

Potassii iodidi		
Potassii bromidi	aa.0	.2
Aquae	200	

To be dissolved and taken, one teaspoonful (5 cc.) three times daily.

In more resistant cases, chloral hydrate was added, in doses of 0.25 gram, according to the following prescription:

Chlorali hydratis	5	
Potassii iodidi		
Potassi bromidi	aa.0	1
Muc. acaciae	30	
Syrupi aurantii	240	
Aquae	ad 300	

Solution to be made, and taken, one tablespoonful (15 cc.) three times daily, after meals.

With these preparations Guggenheimer and Fisher state that they have secured excellent clinical results, though in their preliminary report, case records are not given. They failed to obtain satisfactory response in patients with advanced hypertension and arteriosclerosis, and they excluded from treatment cases with heart failure, because of the slight depressant action of these substances on the heart.

By comparison, the customary 10- and 15-grain doses of bromide and chloral appear enormous. Many clinicians feel, however, that singly or combined, these amounts, repeated if necessary every two to three hours for several doses, are extremely helpful, particularly during an exacerbation of chronic hypertension, with headache, nervousness and insomnia.

A man of fifty years was seen after a digestive upset. His pressure had risen to 200/140, and he was unable to sleep because of severe occipito-frontal headache. He had not been relieved by acetylsalicylic acid and other home remedies. A lumbar puncture revealed clear cerebrospinal fluid under a pressure of 18 mm. Hg. After 10 cc. of fluid had been withdrawn, its pressure fell to 5 mm. The arterial tension nevertheless, was not affected and the headache not in the least relieved. Luminal was given. On the following day, the pressure was 255/162. Chloral and bromide were now prescribed, in doses of 15 grains of each every three hours. After three doses the pressure had fallen to 170/120. After an acute mastoiditis in the

TABLE 14

Drugs used in the treatment of hypertension

SUBSTANCE	DOSAGE	METHOD OF ADMINISTRATION	EFFECT
Amyl nitrite	3 min. ("pearls")	Inhalation	Immediate, transient vasodilatation
Nitroglycerin	$\frac{1}{200}$ to $\frac{1}{100}$ grains	Tablet	
Sodium nitrite	$\frac{1}{2}$ to 2 grains 2 to 4 times daily	Tablet	Rapid, more prolonged, vasodilatation
Erythrol tetranitrate	$\frac{1}{2}$ to 1 grain 2 to 3 times daily	Tablet	
Bismuth subnitrate	5 to 9 grains 3 to 4 times daily	Tablet or powder	Gradual, prolonged vasodilatation
Sodium bromide	5 to 15 grains 1 to 3 times daily	Tablet or elixir	Sedative, vasodilatation
Chloral hydrate	5 to 15 grains 1 to 3 times daily	Elixir	Sedative
Potassium bromide Potassium iodide	aa. $\frac{1}{120}$ gr. (5 mgm.) 3 times daily (with or without chloral hydrate 0.25 gram)	Elixir	Slow, greatly prolonged vasodilatation
Potassium sulphocyanate	$1\frac{1}{2}$ grains 1 to 3 times daily	Tablet or aqueous solution	
Acetylcholine	0.1 gram ampule 1 to 2 times daily	Subcutaneous injection	Rapid, fairly prolonged vasodilatation
Liver extract	0.5 to 5 cc. 1 to 3 times weekly	Intramuscular injection	
Cucurbocitrin	50 to 150 mgm. 1 to 3 times daily	Capsules	

following year his recurrent headache was ascribed by the otologists to a chronic temporosphenoidal abscess, and not to high blood pressure.

Pal (387) regards chloral hydrate as of especial value. He believes that

the nitrites are injurious and has found that morphine relieves only by dulling central sensation. Sometimes, of course, it is invaluable in relieving pain and restlessness. Nitroglycerin is reserved by Pal for anginal attacks. Papaverin, benzyl compounds, the application of heat, including diathermy, and venesection may be helpful in acute hypertension. The last measure is to be repeated with the greatest caution. Liver extract has been found to be without result by Pal, who favors restriction of fluid but opposes Allen's salt starvation. Mattei favors chloral (315).

Gruber's (179) careful pharmacological and clinical studies have been favorable to the temporary depressor action of phenobarbital (luminal), though he found that with prolonged use it grew less and less effective. Its action was not hypnotic, but vasodilator. The claims of benzyl benzoate were not substantiated by his and others' trials, and it appears that cardiac depression is marked (180).

Liver extract in the hands of MacDonald (296, 297) and Major (306) has given successful results, but has not come up to expectations and has lacked uniform action as used by other observers. O'Hare, in 1927, quoted communications from both these workers, Major noting a fall in blood pressure in 40 per cent of his patients, and MacDonald in over 60 per cent, while both found relief from symptoms without fall in pressure in approximately 90 per cent (377).

Insulin has been used (252, 489) for the reduction of hypertension in non-diabetic persons as well as for the relief of angina pectoris. Either a metabolic action or an antagonism to adrenalin is supposed to exist.

Kylin's use of calcium (calcium chloride in daily doses of 1 gram intravenously, 3 to 4 grams by mouth, or 5 to 7 grams by rectum) and atropine in the hope of reducing sympathetic stimulation, has been reported by him to give "extraordinarily satisfactory results." Other workers have used calcium in combination with theobromin and with various endocrine products with varying success. In this country Altnow and O'Hare (19) were not encouraged by their results with parathyroid and calcium-atropine. Andrews (27) has called attention to the difficulty of securing the participation of calcium in the body's metabolic activities, even if enormous doses are given, but in spite of these handicaps he demonstrated its remarkable effect in cutting short attacks of experimental uremia. Major (307) noted the protective action of calcium and potassium chlorides against the pressor substances of the guanidine series, a preliminary intramuscular or intravenous injection of either salt inhibiting vasoconstriction,or causing spasm to subside if the guanidine had been given first. Addison (6) has substituted potassium salts for those of sodium in order to avoid the sodium ion's stim-

ulating or "sensitizing" effect on nerve and muscle tissue. The citrate has been found the most efficient vasodilator. The salts are prescribed in combination as follows:

Potassii bromidi	gr. xx	1.3
Potassii chloridi	gr. xl	2.6
Potassii citratis	gr. lx	4.
Syr. arom.	fl. oz. i	30.

To be dissolved and taken, one tablespoonful, after meals.

O'Hare (377) recommends the use of mistletoe, the French Intrait de Gui, as a vasodilator which particularly alleviates the cerebral symptoms of hypertension. The salicylates are often helpful and for the sufferer who is awakened by the early morning occipital headache, the thermos bottle of hot milk, tea or coffee gives symptomatic relief.

The occasional control of hypertension by the use of thyroid gland is worth remembering. Duden (123) has recently a reported a spectacular example in the case of a woman of fifty-eight years, with arterial tension of 180/130, a basal metabolic rate of minus 35 per cent, a large heart and the T-waves of the electrocardiogram inverted in all three leads. Ten days of thyroid feeding caused the initial cardiac decompensation to disappear and the blood pressure to fall to 130/85. Cessation of thyroid medication a few months later brought a return of the myxedema and the hypertension, but before cardiac failure, so that "high pressure stasis" could be ruled out. With his extensive opportunities for the study of the "myxedema heart," Willius (499) has found little correlation between hypothyroidism and high blood pressure.

There is a further use of thyroid gland in minimal doses in patients with chronic hypertension, obesity, and arthritis. Doses as small as $\frac{1}{10}$ grain three times daily, or $\frac{1}{4}$ grain twice daily, may be given over considerable periods of time with benefit.

Ovarian gland has frequently been given for the relief of hypertension in women who present the vasomotor features of the menopause and there are clinical observations for and against its effectiveness. I have watched its action in a large number of patients, and I am not at all sure that the elixir of sodium bromide does not have just as beneficial results in many cases.

In 1926, Barksdale (50) was led to investigate the virtues of watermelon seed, long used in the form of a tea as a folk remedy for disturbances of urination. He found that its active principle, the glucoside-saponin "cucurbocitrin" had a well marked action in producing vasodilatation and lowering blood pressure.

Barksdale was able to reduce the arterial pressure in 10 cases of hypertension due to tuberculous nephritis, and in 1927 Wilkinson extended the study to 68 patients with vascular hypertension; 56 manifested a favorable result. Althausen and Kerr (17) have treated 40 patients, and in 73 per cent the blood pressure was lowered by 10 mm. or more. There was symptomatic relief in 32 patients. Compared with liver extract (16), which effected a similar reduction of 10 mm. or more in 17 of 27 cases (63 per cent), the action is essentially alike in kind and degree, both being based on sustained peripheral vasodilatation. Patients under fifty years, with known duration of hypertension of less than three years, and free from pronounced renal insufficiency and cardiovascular damage, are most likely to respond favorably. The cucurbocitrin was given by mouth in capsules containing 50 mgm., the optimum dosage being found to be three capsules a day. Larger doses have been given, while a hypotensive effect and diminution of symptoms were sometimes seen after a single oral dose. After the drug was stopped, following its prolonged use, the effects lasted from one to four weeks in 11 cases, and from one to five months in 8 cases.

Another chemical substitution takes place in the case of bismuth subnitrate, which is used by Stieglitz (459) in the treatment of hypertension to "break the vicious circle of vascular fatigue and hyperirritability." There appears to be a continuous absorption of nitrite ions, and a chloride diuresis is produced at the same time that arteriolar relaxation is taking place. Nevertheless, determination of blood chlorides before, during, and after treatment, showed no distinct change related to treatment. Starnotti (456) found that bismuth was not responsible for lowering of blood pressure, and Mehrtens, Hanzlik and co-workers (323), in studying the diuretic action of bismuth, noted a fall in systolic and diastolic blood pressure after the subnitrate and none after the bicarbonate.

French clinicians have applied the vasodilator action of acetylcholine, long known in experimental physiology, to the treatment of hypertension. Villaret and Justin-Besançon (479) and Heitz (194) have recently reviewed the therapeutic results, which are distinctly favorable in patients with functional hypertension. The vasodilatation following the subcutaneous injection of acetylcholine relieves many of the symptoms of general and localized vascular spasm.

In 1924, working upon the theory, partly borne out by his experimental and clinical observations, that cholesterol was the chief of physico-chemical factors involved in the development and persistence of contraction in the smooth muscle cell of the arteriole, Westphal (496) reintroduced sulphocyanate (thiocyanate, rhodan) as an agent for dissolving the cholesterol and

bringing relaxation of the vascular musculature. Occupying a position at the extreme right of the Hofmeister series of anions, the sulphocyanate radical in theory possessed the qualities necessary in order to alter cell membrane permeability and restore normal colloidal action. In 1926,

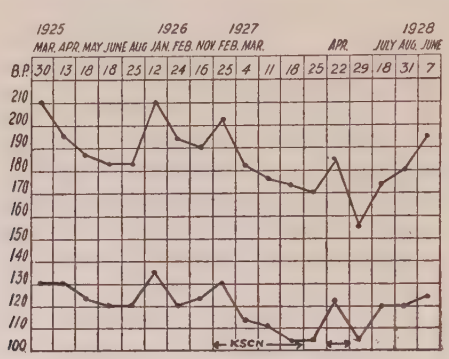

FIG. 3. CHRONIC HYPERTENSION AND CORONARY DISEASE

The patient, a business man of thirty-seven years, thin and nervous, had anginal attacks for one year. The electrocardiogram showed the "coronary T" wave. The record shows clearly the favorable response to medical supervision and the rise of blood pressure when the patient went his own way. Sulphocyanate, in 1927, was more effective than bromide, allonal and other measures. The patient "felt better than for two years." Only one to two anginal attacks daily, and less severe. On March 20, after working hard all day, severe substernal pain, lasting all night. Stopped KSCN for five weeks, with rise of blood pressure. During following year, he has relied on nitroglycerin, and taken little sulphocyanate.

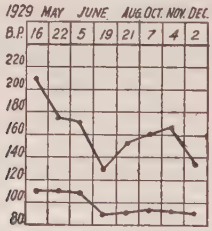

FIG. 4

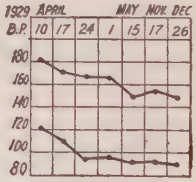

FIG. 5

FIG. 4. CHRONIC HYPERTENSION, SULPHOCYANATE TREATMENT

A woman, aged sixty-one years, housekeeper, relieved of occipital headaches by fall in blood pressure. On exertion, there is substernal oppression, and the electrocardiogram shows T-wave inversion in Lead I. The patient leads an active life, using nitroglycerin for the occasional angina.

FIG. 5. CHRONIC HYPERTENSION, AMBULANT TREATMENT

A woman, aged sixty-six years, complaining of buzzing in the ears, nervousness, occipital headaches. Steady fall in blood pressure and relief of tenseness and symptoms on sulphocyanate ration.

Westphal and Blum (497) were able to report a series of 300 patients who had been treated with sulphocyanate. In only a small percentage did complete therapeutic failure occur. In the great majority hypertension was reduced and symptoms relieved.

By the use of small doses of sulphocyanate, Westphal succeeded in avoiding, in large measure, the side effects which had compelled Pauli, in 1903, and later Pal and Dalmady in 1912, to discontinue its use. Its definite effect in lowering high blood pressure was evident from the first, and in most patients subjective improvement resulted. But there also developed in certain patients, as after the use of bromide and iodide, eruptions of the skin and catarrh of the mucous membranes. Besides these rather minor effects, rapid and sharp reduction in pressure was accompanied by weakness and prostration, and what is taken as further evidence of increased cell permeability was seen in the appearance of psychic disturbances and a tendency for inflammation to arise in various tissues of the body. Because of these untoward experiences, and his own earlier clinical studies, Westphal reduced the amount of sulphocyanate from the 1-gram doses at first given to eventually as little as 0.1 gram three times a day. Even this amount was reduced as the course of treatment and the patient's response indicated. It was noted in certain patients that potassium sulphocyanate produced a greater fall in blood pressure than the sodium salt. Of interest, also, was the observation that withdrawal of sodium chloride from the diet appeared to accelerate the action of the sulphocyanate radical.

Sulphocyanate occurs in the blood of healthy people and is excreted in the urine and saliva. Compared with the normal level of 0.015 to 0.06 mgm. per 100 cc. of blood, Westphal found that the administration of 0.1 gram three times daily led to a level in the blood 0.3 to 0.4 mgm. per 100 cc. in the course of several weeks. The highest value which he found was 0.55 mgm. per cent. When doses of 0.2 gram were given twice to four times daily, the blood sulphocyanate rose to 1 mgm. and in one patient to 1.3 mgm. per 100 cc. of blood. In this case, secondary contracted kidneys and greatly diminished renal function were responsible for this degree of retention, the result of which was the development of pharyngeal inflammation followed by pneumonia. Although the sulphocyanate was stopped in this instance on the eighth day, the level in the blood was 0.6 mgm. after six weeks and had not reached normal several weeks later. In the spinal fluid and in a pleural effusion in this patient, the same elevated content of sulphocyanate was found. The cumulative effect which is likely to occur therefor forbids the use of sulphocyanate in the presence of insufficient renal excretion. With normal kidney function, the excess in the blood is eliminated in three to four weeks.

A further contraindication to the use of sulphocyanate is the presence of active inflammation, lest the increased permeability of the cells augment the inflammatory process, as in the case of unhealed tuberculosis or acute nephritis. On the other hand, isolated casts in the urine and slight loss of the capacity of concentration need not hinder the treatment, nor does slight circulatory insufficiency—digitalis and sulphocyanate may be used jointly.

The therapeutic results obtained by Westphal with sulphocyanate were striking. The fluctuations in blood pressure which underlie many of the symptoms and apparently often incite angiospasm or apoplexy receded under the influence of the drug. There was relief of headache, dizziness, insomnia, palpitation, throbbing in the head, tinnitus, and the pains in joints and muscles of "rheumatism of high pressure." The vasodilatation also caused anginal pain and intermittent claudication to disappear. The effects were obtained in some patients in the first few days, in others not until several weeks of treatment. The extent of blood pressure reduction varied from 20 to 60 mm. or more, and careful observations before and after this fall in tension showed that no decrease in renal function need be feared. Impressed by the practical benefits of sulphocyanate therapy, as well as by the theoretical foundations for its use, I have since used it with equally satisfactory results in patients with uncomplicated genuine or essential hypertension (169). The results in 35 patients have been reported; in approximately 75 cases treated in the past two years, the effects have been similar.

Chemically pure potassium sulphocyanate was prescribed in simple aqueous solution of such strength that 1 fluidrachm (4 cc.) contains $1\frac{1}{2}$ grains (0.1 gram) of the salt. This dose was given in water by mouth three times daily, after meals, for the first week, twice daily for the second week, and then once daily for the third week of treatment. Thereafter the single dose was given daily, or every other day, or was omitted for a week, and the whole course repeated. In obstinate cases, the schedule of two or three doses per day was maintained for several weeks.

In general, I have endeavored to restrict the treatment with sulphocyanate to moderately advanced or fairly early cases; in the advanced stages of hypertensive vascular disease usually encountered in hospital practice, its use has not been attempted with any expectation of benefit. In these patients, vascular reactivity is slight and a fall in blood pressure is likely to mean deficient blood supply in important body areas.

But in persons who come to a cardiac clinic or to the office, there have been few who have resisted entirely the hypotensive effect of sulphocyanate. Fall in pressure of 20 to 60 mm. and relief of symptoms continue to occur

in more than 70 per cent of ambulant patients, even including an outpatient clientele which is frequently difficult to control. The type of patient who will benefit most from vasodilatation has hypertension in which the functional component is pure or predominant (267), and the possibility of successful treatment grows progressively more remote as structural disease of the arteries and arterioles advances. In practice, of course, it is incumbent upon the physician to give border-line patients the benefit of a therapeutic trial, and exceptions are found when arteriosclerotic patients show a distinctly favorable response. One of my earliest patients was a woman, aged sixty-one, with peripheral arteriosclerosis and enlarged heart, who was under the necessity of continuing hard manual labor. Her pressure did not fall until the fourth week of treatment. A persistent hypertension of 220/112 then dropped to the level of 176/98, with a sense of complete wellbeing on the part of the patient.

With the administration of potassium sulphocyanate in small doses and with observation of the patient at weekly intervals, I have seen no ill effects from its use. In several patients early in my experience there appeared a mild drug rash precisely like that of iodide. Since, I have asked patients to stop the medicine upon the development of itching or a skin eruption. There is occasionally a feeling of weakness with the fall in blood pressure, but it is usually transient. I have not seen gastro-intestinal irritation.

Four cases illustrating untoward effects from sulphocyanate have been reported by Palmer and Sprague (389). Their first patient was a man of forty-eight years, without renal insufficiency, but manifesting substernal pain, with cardiac enlargement, gallop rhythm and pulsus alternans. Sulphocyanate was followed by a fall in blood pressure from 220/140 to 170/100. It rose again after the medicine was discontinued. There was weakness and loss of strength during its administration and the patient felt better when not taking it. Digitalis and a reducing diet were of aid. In a man of sixty-four years, with auricular fibrillation and cardiac asthma, there was some relief at first, but later the patient felt better when not taking the sulphocyanate. His blood pressure was 230/130. A woman of forty-three years had rheumatic aortic insufficiency and mitral stenosis. After sulphocyanate, there was a fall in blood pressure and she felt better, but anginal attacks occurred from which she was free when not taking the drug. Their fourth case was that of a woman of sixty-nine years, with blood pressure 250/140. The pressure fell to 170/90 and the patient felt well except for slight substernal oppression on walking.

In the last patient, it would seem that the result of treatment was reason-

ably gratifying and might well contribute toward a more favorable course in spite of the mild anginal symptoms. The patient with rheumatic heart disease and the two men with the terminal complications of hypertensive heart disease are hardly good candidates for treatment.

Exfoliative dermatitis from potassium sulphocyanate has been reported by Weis and Ruedemann (490) and by Ayman (40). The patient of the former was a man of thirty-seven years, with blood pressure 240 systolic, 140 diastolic, signs of thyrotoxicosis and a basal metabolic rate of plus 52. Compound solution of iodine was administered for fourteen days, thyroidectomy was performed, and the patient was discharged in three weeks with a basal rate of plus 1. The blood pressure was unchanged and sulphocyanate was begun. On the eighth day, burning and itching of the skin developed, but the drug was not discontinued until dermatitis appeared on the tenth day. Approximately 40 grains of sulphocyanate had been taken. The face, neck, hands, forearms and ankles were involved, with spread to the chest, back and shoulders. In four weeks the eruption had involuted entirely. Six weeks later, smaller doses of sulphocyanate were given and in three days a mild dermatitis again appeared.

In this patient, renal function had been found normal, but it is clear that there was delay in excretion of sulphocyanate beyond the period of three or four weeks which Westphal found to be the rule. It is a question whether the previous course of iodine shared in producing the cumulative effect.

Ayman's patient was a woman with psychoneurosis and normal blood pressure. She was given 0.6 grams (9 grains) of potassium sulphocyanate daily for eight days, and then developed weakness, abdominal cramps and diarrhea. On the ninth day, a generalized eruption appeared, first on the extremities, next on the trunk and finally on the face. The rash had practically cleared on the sixth day after its onset.

It is to be noted here that double the accepted amount of sulphocyanate was prescribed, and the patient was not seen over a period of eleven days. Until a person's tolerance is established, I believe the patient should be seen once a week, and also that advice be given to stop the medicine if itching or other distress appears. The fact is that the small doses of sulphocyanate appear to be quite large enough to secure satisfactory results, and perhaps they are larger than necessary, if the work of Guggenheimer and Fisher with bromide and iodide is borne out and may be applied to the adjoining members of the Hofmeister series.

One case of sulphocyanate idiosyncracy has been brought to my attention in a young man who also could not tolerate potassium iodide.

In 1925, Nichols (362) described in detail the pharmacologic, toxicologic,

and therapeutic properties of the sulphocyanates, and in conjunction with illustrative case reports, stated that for fourteen years he had used sodium sulphocyanate in the treatment of arterial hypertension with the most satisfactory results. He quoted the older observation of Leroy, in 1909, that "no remedy can or will reduce the blood pressure so kindly or quickly, when given after a proper manner, as the thiocyanates." Nichols found that the alkaline sulphocyanates are stable, distinctive, and biologically active substances, entirely different in their pharmacologic action from the deadly prussic acid and cyanid group.

Two years after this, it was my experience that not uncommonly pharmacists would refuse to dispense the drug in the 2.5 per cent solution until they had been reassured by word of mouth of its harmlessness.

Nichols emphasized the fact that little or no reduction in blood pressure can be expected in patients with advanced structural lesions, but that functional hypertension could and should be lowered in order that the load on the heart and vessels be kept as low as possible. For this purpose he considered sulphocyanate the best drug in use.

In 1928, Smith and Rudolf (451) reported the use of sodium sulphocyanate in 70 patients with hypertension. Twelve patients were given 5 grains three times daily and 11 showed a lowering of blood pressure within thirty-six hours to one week after starting the medicine. Six weeks elapsed in one patient before the pressure returned to its former level after the sulphocyanate was discontinued. In 20 patients 10 grains per day resulted in decided improvement in 10. Five grains per day was given to 40 patients and the blood pressure was lowered in every case in the group, in from one to two weeks.

Logefeil (290) reported 24 patients treated with potassium sulphocyanate with an average fall of 50 mm. in systolic pressure and 25 mm. in diastolic pressure. There was indisputable relief of symptoms.

Palmer, Silver, and White (390) have made clinical use of potassium sulphocyanate in 59 cases of hypertension and secured a reduction of 30 mm. or more in systolic pressure in 42 per cent, and a possibly favorable effect in a larger number. They urge care in the use of the drug in patients with coronary sclerosis, as well as with renal insufficiency.

Askanazy (36), Kramer (257), Lörcher (288) and others (207) report results which indicate the benefit derived from the use of sulphocyanate in properly selected cases. In addition to the potassium salt, calcium sulphocyanate has been used in combination with theobromine. Rhodapurin is obtained by the union of sulphocyanate and caffeine.

Relief of symptoms occurs without lowering of blood pressure in the case of sulphocyanate as with other agents. The following is an example:

F. W. H., aged forty-six years, an executive, was found to have a blood pressure of 180/110 at the age of thirty-four. It has since increased to 230/140. At forty-three years, he began to have occipital headaches almost daily, and a diagnostic study was carried out. His renal function was normal, except for a faint trace of albumin in the urine. At the same time, evidence of a gastric ulcer was found.

In spite of a salt-poor diet, and meat restricted to one meal per week, the blood pressure was unchanged and the headaches persisted. His family physician prescribed sulphocyanate and his headaches disappeared permanently after the second day. A year later I saw him. His blood pressure was 220/140 and there was retinal hemorrhage in one eye, but he was free from symptoms.

On the other hand, cases have come to my attention where great prostration has followed the fall in blood pressure. This I believe should contraindicate sulphocyanate or at least change the method of approach. The factor of cardiac insufficiency is uppermost in many of these unsatisfactory results and digitalis is indicated. In some patients, I have given both digitalis and sulphocyanate, in the first place securing digitalization, and not until the vis a tergo is restored, attempting to diminish peripheral resistance to blood flow.

While the results of sulphocyanate have been almost uniformly satisfactory when the patients were coöperative and the physical obstacles to be overcome were not too great, it is not a panacea for hypertension. It does not supplant any of the fundamental hygienic and dietary measures for the control of high blood pressure, and its ultimate action on the arteriolar smooth muscle cell may not be different from the effect of weight reduction or other means of influencing cellular metabolism. One method of approach may supplement the other, and while the physiologist is exploring a difficult terrain, it is of some value, I believe, that the clinician has the means at hand, by various agents, to modify, in some degree, the substratum of hypertension, and thereby ease his patient's symptoms and overburdened circulation.

Other measures, foreign proteins (104), vaccines (65), hydrotherapy, high frequency current, diathermy (477), carbon arc radiation (273), radium emanation intravenously (10, 350) offer nothing of sure value or advantage in the treatment of persistent hypertension.

Firnbacher (152) found no difference in the effects of baths in plain warm water compared with carbonated water or the "pine needle" bath. He re-

gards artificial hyperthermia as too severe a form of treatment. While the therapeutic outlook in the case of permanent hypertension is extremely unsatisfactory, he states that labile hypertension offers a favorable prognosis and responds to the use of bromides, nitrites, diuretics, baths and venesection. These temporary measures, however, must be supplemented by physical and psychical repose.

Westphal (497) warns against the possible pressor effects of hot baths (inverse reaction to warmth) in producing the conditions for apoplexy.

Zimmern (501), who in 1912 was one of the pioneers in the roentgen radiation of the suprarenal region in patients with hypertension and reported favorable results at that time, has recently, with Baude, reviewed the status of this method. While the results of empirical treatment sometimes have been excellent, it is concluded that the method of animal experimentation is not likely to yield useful information in this field and that in respect to human patients the subject is still vague. The doses used are much too small to be expected to bring structural changes in the suprarenals and an influence on the neuro-vegetative system is suggested. Practically, it is agreed that tumors of the suprarenal gland invite surgery, and not radiation; while the results of treatment directed toward the suprarenal glands are unconvincing.

When hypertension follows mechanical obstruction to the outflow of urine, for example in prostatic hypertrophy, removal of the gland or even the use of a catheter of the indwelling type may restore diuresis and normal blood pressure. A man of fifty-four was recently admitted in uremic coma and died who apparently had been in good heath until a chill two weeks before ushered in oliguria and at length complete suppression. Extreme dehydration was regarded as partly responsible for a white blood count of 88,700, and a non-protein nitrogen level of 277 mgm. per 100 cc. of blood. The principal anatomical finding was the prostatic enlargement, with hydronephrosis. In chronic pyelonephritis Braasch and Cathcart (82) found increased blood pressure, retinal changes and reduction in urinary output only as terminal complications. Yet Friedrich Müller (351) states that the highest pressure he ever saw—340 mm. Hg—was in a patient who had pyonephrosis. Lavenant (275) has found remarkable lowering of pressure following removal of obstructions in the urinary tract, and Keith emphasizes the value of intravenous injection of normal salt solution or 10 to 20 per cent glucose solution in treating dehydration as it occurs in terminal uremia. Apparently hopeless patients are sometimes restored (241a).

When a comatose patient is seen for the first time, and the blood pressure is high, the condition of pseudouremia or cerebral angiospasm has to be

considered. Lumbar puncture is likely to be helpful in these patients, but the pressure of the cerebrospinal fluid should be reduced slowly. A manometer is advisable, but it has been found that if a 22-gauge needle is used a flow of forty drops per minute roughly indicates normal pressure.

The hypertension of eclampsia is regarded by Stander (455) as a protective mechanism. Venesection is opposed, and lumbar puncture has been found unsatisfactory. Stander quotes the analysis made by Williams of the comparative results of radical and conservative methods of terminating pregnancy. Among 110 cases in which radical measures were carried out, maternal mortality was 22.8 per cent, compared with a death rate of 13.6 per cent in 198 women treated conservatively. If Caesarean section is to be done, local or spinal anesthesia is indicated. The use of heparmone in the hands of Miller (quoted by Stander) has given a mortality of 6.9 per cent in 43 consecutive cases of eclampsia.

At the suggestion of Allen, a series of 13 pre-eclamptic patients was treated by Bland and Bernstein (70) with salt-free diet. In 11, the blood pressure dropped to normal, and in all relief of symptoms was obtained.

Abel's plasmaphaeresis has been applied by Irving (219) to the treatment of eclampsia in 15 cases. A liter of blood is withdrawn and thereby the theoretical toxemia is reduced by approximately 20 per cent. After the corpuscles are centrifuged and washed, they are reinjected suspended in isotonic salt solution. In 10 patients with eclampsia and pre-eclampsia, there was reduction of blood pressure and albuminuria, and temporary improvement resulted in chronic nephritis.

It remains to consider briefly the treatment of cardiac failure and renal insufficiency in the course of persistent hypertension.

Digitalis is never contraindicated by any degree of hypertension, and not rarely an increased blood supply to the medulla will have the effect of lowering systemic pressure. Rest in bed is perhaps as important as digitalis.

The Karell diet is a simple and often effective measure of relief. In acute decompensation, with venous distention and paroxysmal dyspnea, Volhard (483) puts the patient in bed, gives magnesium sulphate to clean out the intestinal tract, limits fluids and withholds food. After a twenty-four-hour fast, strophanthin with salyrgan is given. Volhard recommends euphyllin and warns against morphine in the presence of periodic breathing. For paroxysmal dyspnea, however, many will agree that morphine is the drug of choice. Venesection in congestive heart failure may reduce the high pressure for a few hours. Many conservative men appear now to oppose its use: Morawitz (333) and Pal (387) urge restraint in blood

letting. Alvarez (24) reports a case where venesection produced a sense of impending death. The pressure fell from 280 mm. to 120 mm., followed by weakness for months. Kahler (235) favors venesection because it lowers the burden of the circulation, removes toxic products, and causes reflex dilatation of the vessels. Allbutt spoke of the beneficial effects of venesection both in crises and in some patients as a routine twice a year. Eyster (138) studies venous pressure as a guide to withdrawal of blood.

Grafe (177) opposes the indiscriminate use of venesection, but in occasional patients has found that the removal of 500 cc. of blood is followed by relief of headaches and dizziness for a period of several weeks.

Musser (354) has reported favorable effects from the use of theophylline-ethylenediamine (0.1 or 0.2 gram three times a day) in hypertensive heart disease, especially where angina is a factor.

In the treatment of hypertension in nephritis, Foster (161) sounds an optimistic note: In many cases the characteristic tendency to store in the tissues the nitrogenous bodies which should be secreted may be combated with success if a low protein diet (30 grams daily) is persisted in for a couple of months. "The blood pressure becomes definitely lower, along with an improvement in the general condition of the patient and an increase of his strength and his ability to withstand fatigue."

My own experience with true nephritic hypertension of persistent type has not been encouraging. With fixed high pressure, extensive retinitis, and greatly diminished phenolsulphonephthalein excretion, the prognosis of chronic nephritis as it is seen late in its course is uniformly unfavorable. Rather must there be early recognition and effective prophylaxis and treatment of acute nephritis. I have just seen in the clinic for outpatients a negro university student of twenty-five years who with much sacrifice and labor has gone through college and half way through law school. He has had tonsillitis for several winters. Five years ago he was advised to have the infected tonsils removed. When he returned to school in the fall, he found that his vision was blurred and headaches followed attempts to study. His examination showed extensive retinal exudation and vascular changes, blood pressure of 220/130, albumin and casts in the urine, and phenolsulphonephthalein excretion of 20 per cent in two hours. His tonsils have been removed, his teeth are in process of treatment, and his diet is restricted. All too late!

It is in acute nephritis that treatment is successful when rest, diet and removal of infectious foci can be thoroughly controlled. Rest should mean staying in bed, as Boyd (81) insists, until all acute symptoms and signs have disappeared. Too often the child with acute nephritis is allowed up when

partly cured only to suffer a relapse and go on to chronic nephritis. Diet is restricted in protein in order that there may be no retention of nitrogen. Fruits, vegetables and milk are given that acid-base equilibrium be maintained. When all but traces of albuminuria have disappeared, the protein may be raised to 50 or 60 grams with eggs and meat, bread and cereals, but months should elapse before a return to normal protein and salt-containing diets is allowed.

In the absence of pronounced cardiac or renal insufficiency, surgery in the hypertensive patient is without especial danger. Rather than being contraindicated by high pressure, the removal of a source of disability or irritation—hernia, myoma uteri, cholelithiasis—may be advisable as a means of benefiting the patient's general health and his prognosis. Preoperative and postoperative care are of extreme importance. Abdominal distention I have seen exercise unfortunate effects in the case of coronary artery disease. Inhalation, rectal, spinal and local methods permit a wide choice of anesthesia for the particular patient (379, 325, 467). During operation there are no significant changes in blood pressure nor in heart action (321).

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INDEX OF PERSONAL NAMES

Abel, 124
Adams, 38
Addis, 7, 11, 85
Addison, 45, 113
Allbutt, ix, 1, 56, 67, 94, 125
Allen, E. V., 40
Allen, F. M., 42, 102, 104–106
Althausen, 115
Altnow, 45, 113
Alvarez, 46, 52, 60, 125
Ambard, 33, 42
Amberg, 30, 54
Anderson, 36
Andrews, 113
Anitschkow, 37, 43
Anrep, 29
Antoine, 31
Archer, 62
Aschoff, 4, 7, 18
Ashe, 32
Askanazy, 21
Aubertin, 39
Ayman, 120

Backman, 37
Baehr, 15
Bailliart, 32
Baker, 29
Barach, 16
Barath, 54
Barker, 39
Barksdale, 114
Barrieu, 81
Bartels, 11
v. Basch, 6
Baude, 125
Bauman, 39
Beaujard, 42
Beckmann, 14
Bell, 18, 46, 90
Bennett, 72
Benni, 70
Berger, 42, 104
Bernard, 94
Bernstein, 124
Billingsley, 29
Bishop, 56
Bland, 124
Blankenhorn, 74
Blau, 34
Block, 31
Blum, 116
Boas, 77
Böhm, 46
Bolliger, 83
Bordley, 29
Bowes, 54
Bowers, 90
Boyd, 125
Braasch, 123
Bradford, 11
Branch, 54
Bright, 1, 6, 11, 33, 90
Broadbent, 80
Brown, 12, 32
Bundesen, 74

Campbell, 74
Cash, 37
Cathcart, 123
Chauffard, 33, 43
Christian, 56
Clark, 37
Claude, 31
Clawson, 18, 46, 90
Conner, ix
Cooper, 26
Corwin, 47
Crowell, 41
Cushing, 29
Cutler, 29

Dale, 14
Dalmady, 117

Danzer, 34
Dawson of Penn, 28
Diehl, 52, 75
Donnison, 25
Dragstedt, 41
Draper, 65
Duden, 114
Dumas, 33
Dumas, A., 108
Durig, 10

Edens, 50
Ehrström, 90
Ellis, 92
Eskelund, 84
Evans, 15, 16
Eyster, 87, 125

Faber, 11
Fahr, G., 52, 79
Fahr, T., 11, 15, 19, 90
Fahrenkamp, 45, 74
Fahrion, 17
Falta, 33
Fineberg, 42, 76–77, 104
Firnbacher, 122
Fishberg, 19, 31, 34, 59
Fisher, I., 110, 120
Fisher, J. W., 89
Fleming, 109
Foster, J. H., 26
Foster, N. B., 12, 16, 34, 39, 67, 81, 100, 125
Franck, 28
Friedenwald, H. and J. S., 71
Frost, 76, 80
Fulton, 77

Galen, 6
Garrod, 33
Geisböck, 32
Gelman, 46, 50, 53
Giffin, 32
Goldzieher, 40
Grafe, 104, 125
Groedel, 32
Gruber, 113
Guggenheimer, 110, 120
Gull, 7

Härle, 29
Hales, 5
Hamman, 50, 90
Hanzlik, 115
Harpuder, 15, 49, 81, 90
Hartman, 19
Harvey, 6
Heimberger, 21
Heitz, 115
Helmholtz, 68
Hench, 30
Herrick, 37, 39, 47
Herzog, 14
Hill, 6
Hitzenberger, 34, 38–39
Högler, 41
Hooker, 13
Hopkins, 46
Horder, 102
Horine, 93
Hoskins, 41
Huchard, 22
Huddleson, 105
Hübener, 21, 81
Hueck, 18
Hülse, 19, 34, 41
Hunter, 2, 3, 89
Hurlin, 27, 40
Hutchinson, 65

Irving, 124
Ismail, 26

Jackson, 34
Janeway, ix, x, 8, 37, 40
Jansen, 44
Johnson, 7, 15, 33
Joslin, 38

Kahler, 22, 31, 39, 125
Karn, 28
Kauffmann, 60, 62, 73, 80
Keith, 18–20, 70, 90, 123
Kelman, 36
Kernohan, 20
Kerr, 115
Kilgore, 72
King, 80
Kinney, 74

Kirkes, 7
Klemperer, 20, 92
Koch, 14
Koessler, 36
Korotkoff, 6
Kramer, D. W., 39
Kramer, R., 257
Kraus, F, 22, 45
Krogh, 13
Kylin, 13, 14, 33, 39, 44, 62, 73, 74, 113.

Labbé, 44
Lamache, 31
Landerer, 21
Lange, 14, 21, 30, 39, 64, 78, 81
Langstroth, 103–104
Lavenant, 123
Lébec, 54
LeConte, 46
Lee, 52
Lees, 75
Lehfeldt, 46
Lemierre, 34
Leroy, 121
Levine, 77,
Lewis, 13
Lian, 81
Libman, 56,
Linder, 54
Löhlein, 7
Lörcher, 121
Löwenstein, 45
Logefeil, 121
Lombard, 13
Long, 15
Ludwig, ix, 1, 3, 5, 7
Lundberg, 14

MacCallum, 16
MacDonald, 113
MacKenzie, 56, 107
MacLean, 30
Magniel, 54
Mahaim, 81
Mahomed, 5, 8, 60, 90
Major, 33, 34, 39, 113
Malpighi, 6
Mannaberg, 80
Marañon, 38, 39
Marey, 5
Marrack, 92
Marsh, 37
Master, 39
Mattei, 173
Matthes, 45
May, 89
Mayers, 52
McClure, 41
McLester, 42, 100, 101, 104
McWilliam, 98
Mehrtens, 115
Miller, 106
Miller, Joseph L., 107
Mitchell, 67
Moog, 54
Morawitz, 107, 124
Moschowitz, 17, 28, 100
Mosenthal, ix, 37, 40, 42, 75, 87, 100, 104
Mosler, 37
Mühlmann, 30
Müller, C., 74
Müller, F., 12, 46, 123
Müller, O., 13, 17, 21, 81
Munk, ix, 9, 12, 14, 18, 46, 63, 83, 101
Musser, 125
Mylius, 69

Naffziger, 109
Nesterow, 21
Neubauer, 33, 38
Newburgh, 37
Nichols, J. B., 120–121
Nichols, E. G., 32
Nielson, 46
Nobécourt, 54
Nonnenbruch, 13
v. Noorden 38
Nuzum, 37
Nyiri, 83

O'Hare, 19, 42, 45, 69, 75, 100, 104, 107, 113
Ohler, 60
Ophüls, 16
Oppenheimer, B. H., 31, 59
Oppenheimer, E. T., 39

Oppenheimer, R. H., 31
Osler, 72
Otani, 20, 92

Paget, 93
Pal, 64, 69, 113, 117, 124
Palmer, 64, 119, 121
Pauli, 117
Paullin, 37, 79, 100
Peckham, 47
Peiser, 29
Pellissier, 46, 54
Peters, 203
Petersen, 45
Pfalz, 31
Piersol, 90
Poiseuille, 5
Polak, 46
Post, 16
Potain, 1, 37
Prevost, 33
Pribram, 43

Randolph, x
Ransom, 29
Rappaport, 107
v. Recklinghausen, 6
Renault, 31
Richard, 44
Richter, 54
Richter-Quittner, 34, 39
Ricker, 7, 14, 69
Riegel, 13
Riesman, 46
Riseman, 50
Riva-Rocci, 6
Roddis, 26
Roe, 44
Roesch, 44
Rogers, 3, 89
Rogoff, 41
Rolleston, 101, 110
Romberg, 11
Rosenthal, 20, 91
Rosselet, 81
Rowntree, 12, 32, 76
Rudolf, 121
Ruedemann, 120
Ryle, 8

Sachs, 15
Saller, 50
Sansum, 102, 108
Schönheimer, 43
Schlesinger, 46
Schmidtmann, 443
Schur, 33, 40
Schwartz, 53
Shapiro, 77
Shaw, 109
Sherrill, 42
Short, 42
Sigler, 74
Silver, 121
Smith, A. G., 121
Smith, F. M., 78
Sprague, 119
Stahl, 28
Stander, 48, 124
Starling, 29
Starnotti, 115
Stettner, 15
Stewart, 40, 41
Stieglitz, 16, 42, 47, 115
Stivelman, 53
Stockard, 53
Stocks, 28
Straub, 102
Strauss, 33
Strouse, 36
Sutherland, 52
Sutton, 7
Swift. 15
Symonds, 40, 88

Terry, 39
Thayer, 93
Thölldte, 44
Thomas, 44
Thro, 44
Tigerstedt, 10
Traube, 1, 7, 56
Tung, 26
Tychowski, 41
Tzanck, 31

van Leersum, 43
van Slyke, 12
Vaquez, 57, 101
Verworn, 14
Vierordt, 5
Villaret, 115
Vogel, 42
Voit, 54
Volhard, 1, 9, 11, 19, 22, 34, 90, 107, 124

Wagener, 19, 71, 72
Walker, 42, 104
Wassermann, 64
Weber, 30
Weis, 120
Weiss, 50
Wertheimer, 13
Westphal, 12, 21, 39, 43, 44, 115, 117–120, 123
White, 64, 121
Widal, 33
Wiesel, 33, 40
Wiggers, ix
Wildt, 54
Wilkinson, 115
Williams, 124
Willius, 93, 114

Yater, 72

Ziegler, 7
Zimmermann, 46
Zimmern, 123
Ziskin, 81
Zondek, 44

SUBJECT INDEX

Angina pectoris, cause of acute hypertension, 59; cause of death, 90; use of nitroglycerin in, 113; theophylline-ethylenediamine in, 125
Anthropometry, 60, 65
Aorta, coarctation of, 74; hypertensive vs. arteriosclerotic changes in, 78, 79
Aortic insufficiency, cause of systolic hypertension, 23, 76; relative, from dilatation, 79
Arteriocapillary fibrosis, 7–8, 15
Arteriolar, function as neuromuscular organ, 14, 97; morphology, 7, 13; intimal hyperplasia, 18, 19; muscular hypertrophy, 18, 19; necrosis, 14, 18; spasm in eclampsia, 69; and after guanidine, 35; "throttling," 21
Arteriolosclerosis, contrasted with arteriosclerosis, 18, 69, 72; distribution, 18; result of vascular strain, 18; retinal, 69–72
Arteriosclerosis, antagonism to hypertension, 64, 65; causes, 16; generalized, 16; splanchnic, 16; medullary, 29; pure, 64
Arthritis, 61, 62

Bacterial toxins, 36
Biopsy, shows arteriolar hypertrophy, 20, 37
Blood amino-acids, 34, 37; calcium, 44–45; cholesterol, 12, 43–44; constituents of, 35; creatinin, 32; guanidine, 34–36, hemoglobin and red cells, 32; non-protein nitrogen, 33; polypeptides, 34; potassium, 44–45; sugar, 37–39; urea, 33, 34; uric acid, 33, 34, 47, 90
Blood flow, in arterioles and capillaries, 21–22, 64; obstructed in damaged kidney, 7; peripheral resistance to, 1, 21
Blood pressure, adrenalin reactions, 45; diastolic pressure and coronary blood flow, 78; factors in maintaining, 1–2; fixation of, 2, 23, 25, 73; reduction of, cause of angina, 119; effect on cerebral circulation, 108, 109; effect on renal function, 110, 118; effect on symptoms, 98, 121; standards and normal limits, 2–4; variability, 2, 4, 73–75
Blood sedimentation, 32
Blood surface tension, 32
Blood velocity, 2, 76
Blood viscosity, 2, 32
Blood volume, 10, 12, 30
Body weight, relation to blood pressure, 37, 39–40
Bright's disease, cardiac hypertrophy in, 6; definition of, 7; tense pulse in, 1, 7, 17

Calcium, diuretic action, 44; inhibits guanidine, 113; relation to sympathetic system, 45; therapeutic use, 45, 113
Capillaritis, 14
Capillary, function, 10, 14, 64; morphology, 14; reflex effects, 14; "spastic" and "spastic-atonic" complexes, 22; tension, 14, 21
Cardio-respiratory test, 80; types of reaction, 81
Causes of death, 90–94
Cell permeability, 43, 45
Cerebral circulation, 28–32
Cerebral hemorrhage, 91, 92
Chemical constituents of blood, 35
Cholesterol, 43–44, 115
Clinical study, scheme of, 86–87
Constitution, 22, 64–65
Coronary sclerosis, 66
Coronary thrombosis, 80
Creatinin, 33; test for renal function, 35

Dehydration, intravenous salt and glucose in, 123
Diabetes, 38–39

Diet, 100, 102–109; acid vs. alkaline ash, 37, 102, 104, 108; excessive carbohydrate, 100, 104; cholesterol, 37, 104, 115, 43–44; coffee, 26; corrective (vitamine) 102–104; eggs, 104; high protein, 26, 36; Karell, 109, 124; liver, 37, 104; low protein, 36, 125, 126; for obesity, 40, 104; salt-free, 42–43, 100, 102, 105, 108; water, 106, 107
Digitalis, 118, 122, 124

Eclampsia, arteriolar spasm, 69; conservative treatment, 124; constitution, 65; metabolic findings in, 48; plasmaphaeresis, 124; salt-free diet, 124; sequelae, 47; symptoms and signs, 57–59
Edema, 12, 68, 71, 104
Electrocardiography, in diagnosis and prognosis, 81, 93
Encephalopathy, hypertensive, 31, 59
Epinephrin, 40–41, blood pressure reactions to, 45; use in acute hypotension, 109
Eugenics, 97, 99
Exercise, 63, 100, 101

Fluoroscopy, of heart and aorta, 78

Gastric function, 61, 64
Guanidine, 34–36

Heart, aortic insufficiency, 79; arrhythmias, 80; in arteriosclerosis, 78; auriculoventricular block, 80; bundle-branch block, 93; intraventricular block, 80; congestive failure and high pressure, 54, 59; functional tests, 80, 86, 99; gallop rhythm, 80; incidence of hypertensive disease, 50–52; myocardial changes, 66, 77–81; paroxysmal dyspnea, 64; prognosis, 92, 93; pulsus alternans, 80; relative mitral insufficiency, 52, 79; roentgen study, 78, 81; tachycardia, 80; treatment of failure, 124–125
Heredity, 22, 59–60, 62, 64, 99
History, 67, 86
Hyperpiesia, 1; "crises," 109

Hypertension, acute, 31, 57, 59; anatomic, 23; benign, 2, 57, 88; in brain abscess, 30; in brain tumor, 30; cardiac, cerebral and renal types, 61–63; as cause of heart disease, 50–51; in diabetes, 38–39; diastolic, criteria of 3, 4; factor in coronary blood flow, 78; factors causing, 76, 77; prognosis of, 90; with increased metabolic rate, 77; disorders of sexual organs in, 46; in eclampsia, 47; extrarenal nature, 9, 13; familial, 62, 64; fixation, 2, 23, 25 73; functional, 23, 57, 119; infection in, 16; malignant, 20, 44, 70, 78, 92; in meningitis, 30; paroxysmal, 11, 30, 57; primary (essential) vs. secondary, 2; progressive nature of, 50, 76, 98; psychic factors in 24–28, 63; pulmonary, 2; pure, 21, 64, 76, 81; "red" and "white," 22; "solitaire," 56; symptoms, prehypertensive, 8, 21, 56, 60–61; syndromes of, 61–64; valvular heart disease and, 77; variability, 4, 73–75; "virtual," 69, 80
Hypertonia, 1
Hyperventilation, 7, 107
Hypocalcemia, in pregnancy, 47
Hypochondria, avoiding, 72, 94

Incidence of hypertension in, African and American negroes, 25, 48; aged, 54–55; applicants for insurance, 52; children, 53–54; Chinese, 26; Egyptians, 26; hospital patients, 26, 48; laborers vs. brain workers, 53, 102; lead workers, 52; tuberculous, 53; schoolboys, 28; university students, 52, 75

Kidney, classification of diseases of, 7, 8, 11, 19; effects of quantitative reduction and extirpation, 9, 11, 36, 37; functional tests, concentration and dilution, 83–84; excretion of solids, 81–84; of phenolsulphonephthalein and sodium thiosulphate, 82, 83; of protein, cells and casts, 7, 85

Longevity, effect of hypertension on, 88–90
Lumbar Puncture, 32, 107, 108, 124

Menopause, 46
Myomata uteri, 46
Mortality, 2–3, 52, 88–94

Nephritis, definition of, 7; capillaritis in, 14; a general systemic disease, 13, 22; lesions in, 19, 85; infection and immunity, 15; prenephritic rise of blood pressure, 13; retinal changes in, 68, 71; urinary findings in, 85; treatment, 125
Nephrosclerosis, relation to infection, 16; result of vascular strain, 9, 15, 18; separation from secondary and senile contracted kidneys, 17–18; urinary findings in, 84–85
Nephrosis, 10, 12
Nitrogen balance, 103

Obesity, 27, 37, 39, 40, 62, 102, 104, 105, 107
Occupation, 28, 53, 93, 100, 133
Ophthalmoscopy, 11, 68–72, 86
Ovarian function, 46

Paroxysmal, dyspnea, 64; hypertension, 11, 30, 57
Philosophy of life, 26, 94, 97, 100, 107
Pituitary gland, 65
Plethora, 6, 32
Polycythemia, 32
Potassium, 44–45, 113
Prognosis, from albuminuria, 3, 92; from urea, 34; from cardiac function, 92; causes of death, 93; modes of death, 90–93; influence of diastolic pressure, 76, 90; electrocardiographic changes, 93; influence of systolic pressure, 89–91; in malignant hypertension, 20, 92; from retinal lesions, 68, 92
Prostatic obstruction, 123
Pseudouremia, 31, 59, 63
Pyelonephritis, 125

Relaxation, 28, 100, 101
Renal function, 84–85
Renal insufficiency, and anemia, 32; relation to hypertension, 82; prognosis of, 90–92
Retinal hypertensive disease, 68–72

Scarlet fever, 54
Sodium chloride, 42–43, 102, 104–106; substitution of malate, 106
Sphygmograph, 5, 8
Sphygmomanometer, 5, 6; graphic, 80
Suprarenal, glands, removal of, 40; medulla vs. cortex, 41; radiation, 57, 103; tumor, 40, 57; veins, hypertrophy of, 40
Surgical operations, 123, 126
Symptoms, prehypertensive, 8, 56, 60
Syndromes, 61
Syphilis, 53, 54

Thyroid gland, use of, 114
Thyrotoxicosis, cause of systolic hypertension, 76
Treatment, acetylcholine, 115; advisability of reducing hypertension, 98, 107, 109, 119; aim of using drugs, 110; baths, 122, 123; bismuth subnitrate, 115; calcium, 45, 113; change of habits, 95, 100; chloral, 111, 113; cucurbocitrin, 115; exercise, 100–101; insulin, 113; iodide and bromide, 110–111; ion substitutions, 45, 106, 113; liver extract, 113, 115; mistletoe (gui), ovarian gland, 114; phenylbarbital, 113; potassium salts, 113–114; radiation, 122; radium emanation, 122; reduction of blood pressure, ill effects of, 108–109, 119; relief from, 98, 121–122; relaxation, 88, 100–101; salyrgan, 124; sulphocyanate, 118–121; accumulation in blood, 117; dermatitis from, 120; dosage, 118, 120; effects on blood pressure, 122; on coronary circulation, 119; on renal function, 118; on symptoms, 118, 122; theophylline-ethylenediamine, 125; thyroid, 114; Trinkkur, 106; water and salt deprivation, 107

Urea, 33–34

Uremia, calcium in, 113; dehydration and intravenous therapy, 123; factor in mortality, 18, 82, 90; hypertension and, 82; toxic retention in 9, 34

Vascular reactivity, 10, 73, 98, 107, 121
Vasoconstriction, primary factor in hypertension, 2, 9, 10, 21–22; control of, 97; in uremia, 59
Vasomotor regulation, 29; instability of, 54, 74, 99
Vasoneurosis, 8, 22, 60
Venesection, ill effects of, 125; in congestive heart failure, 124–125; relief from, 125; routine use of, 72, 125
Venous pressure 31, 87, 107, 125

Weather and circulatory deaths, 74

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